vfa Reflection paper
"Complex Study Designs – Relevance for Advances in medicine"

EXECUTIVE SUMMARY

The results of high quality clinical trials are the basis for demonstrating the efficacy and safety of new treatment options and thus are the preconditions for the regulatory approval process. These results also form the groundwork that evidence-based medicine rests on. However, the standard approach for obtaining this evidence – a series of randomized controlled clinical trials (phase I to III) including an investigation of one or more interventions in a single indication parallel at the same time with a random distribution of patients into the groups – has been shown up to run against its limits more and more often. Furthermore, the classical trial designs often do not permit the desired rapid translation of basic scientific findings into applied clinical and medical practice.

An important reason for this is the continuous progress being made in elucidating the molecular causes of disease. This lays the groundwork for developments in precision or personalized medicine. It is now possible to differentiate medical conditions and patient subgroups even further and to identify molecular targets/target structures that are amenable to treatment.

Thus, the evolving scientific knowledge of disease causes requires the use of complex study designs. For these reasons, there is a high interest by the pharmaceutical industry to closely cooperate with both the regulatory authorities and ethics committees (that approve the conduct of clinical trials/grant their favourable opinion, respectively) and HTA bodies in developing and implementing these study designs. It should be explored in joint discussions what the requirements for approving and assessing these study designs are. First steps into that direction have already been taken, see article by Keller-Stanislawsky *et al.* in Bulletin zur Arzneimittelsicherheit; edition June 2017: http://www.bfarm.de/SharedDocs/Downloads/DE/Arzneimittel/Pharmakovigilanz/Bulletin/2017/2-2017.pdf?__blob=publicationFile&v=6

In the following, a couple of complex trial designs, basic approaches and considerations will be presented. To establish these complex study designs in applied medical care and guarantee their appropriate use a comprehensive discussion with all relevant stakeholders is necessary.

Hausvogteiplatz 13
10117 Berlin
Telefon 030 206 04-0
Telefax 030 206 04-222
www.vfa.de

Content

A) Background

In addition to the proof of quality, evidence of the efficacy and safety of a new therapy - which must result from the results of clinical trials - forms the basis for the approval of novel treatments and for evidence-based medicine. Randomized clinical trials (RCTs) are the recognized gold standard for this.

Advances in Research Raise New Questions

In the view of the vfa, it is clear that in the interests of the patients the stringent standards that are currently in force should be maintained. The advances in research raise new questions in the development and make for some investigations new processes in the design of RCTs necessary. The classical standard approach for obtaining this evidence consists of a clinical trial program (neatly differentiated into the phases I to III) that investigates one or two interventions in a single disease in a group of patients. All too often, the classical study designs run methodically against their limits. Additionally, simple study designs in oncology, but also other indications, fail to satisfy the requirement of rapidly translating basic scientific findings into applied clinical practice. One important reason for this is that continuous progress being made in elucidating the molecular basis of disease. Also new approaches like novel effect mechanisms e.g. immune oncological approaches are entering the field.

These new approaches permit to further differentiate medical conditions and patient groups based on biomarkers and allows the development of novel drugs and improved drugs with an optimized efficacy and safety profile. In other words, it allows to apply a stratified or, ideally speaking, personalized treatment approach (precision medicine).

It is therefore not surprising that in clinical research there is a clearly observable trend to assess and increasingly to use biomarkers in clinical trials (www.clinicaltrials.gov) – see also "Medical Biotechnology in Germany 2015", vfa bio/BCG or Informa UK Ltd. 2014; Scrip News; scripinteligence.com, May 2014. On the other hand, we are faced with new challenges in conducting these clinical trials. These concerns in particular the planning and design of clinical trials, recruitment (molecular testing or genotyping of large sample sizes to identify the small pool of patients that is eligible for the approach under study) and the conduct of these clinical trials as a whole. For this reason, complex study designs are important e.g. to be able to evaluate biomarker-based hypotheses in clinical trials in an appropriate and comprehensive way and to develop or validate new treatment approaches.

Challenge to the System as a Whole

It is the system as a whole (academic and industry research & development, regulatory authorities, ethics committees and the HTA bodies) that must face up to these challenges rather than focusing exclusively on classical study designs. If not, all medical stakeholders run the risk that key clinical questions that are raised in connection with novel treatments and diagnostic options remain unanswered and are not fully explored.

There is also a growing interest in conducting mechanism-based clinical trials, where treatment decisions that need to be taken during a clinical trial are based on criteria other than the traditional definitions of diseases that have been used in the past. Methodological innovations that are geared towards these requirements will include combined approaches, e.g. more than two treatments in more than one type of patient or disease entity. Complex study designs enable to establish a comprehensive evaluation while resting in the same trial structure and they allow sub-studies in a master protocol to answer novel questions in the setting of a RCT.

Complex Study Designs increasingly gain in Importance

Complex study designs are based on one overarching trial protocol that enables to answer multiple questions within the framework of a single trial. These approaches allow to investigate one or several interventions in single or multiple diseases and to target a specific biomarker defined subpopulation or disease subtype.

Besides the advantage of potential insights coming from complex study designs there also exists the risk of distortions concerning the results (bias) that may be difficult to handle in a clinical trial. Examples could be a misinterpretation of effects but also problems monitoring the clinical trials. Moreover, with these study designs, the statistical inference of the results is based on considerably smaller sample sizes and the risk of reducing the safety data set has to be weighed up carefully against the expected positive effects.

It should also be discussed what degree of scientific uncertainty regarding patient cohorts, dosing of the investigational product, concomitant therapy and/or suitable primary endpoints is acceptable from both a clinical and an ethical standpoint before commencing exploratory or confirmatory clinical trials.

In the view of the vfa, complex study designs are of hallmark importance in advancing progress in medical science. Therefore, there is high interest to jointly establish procedures that allow for the approval and consistent assessment of these study designs based on mutually recognized criteria in cooperation with the federal higher authorities and ethics committees that must approve

the conduct of clinical trials/grant their favorable opinion, respectively, and the HTA bodies.

B) Examples of Complex Study Designs

Adaptive Trial Designs

The difference between an adaptive trial design and the design of a classical phase III trial is that data collected during the course of the program is used to amend the trial protocol prospectively (referring to modifications defined by protocol and linked to results from intermediate assessments), e.g. based on the results of other trials running in parallel, new scientific findings or data from the current clinical trial.

Possible, prospective planned adaptions are e.g.:

- Opening new treatment arms,
- Closing ongoing treatment arms,
- Changing inclusion and exclusion criteria,
- Modifying the study population with respect to the disease under study (e.g. based on molecular subtypes or predictive markers),
- Changing the required sample size,
- Changing the dosing of the investigational product,
- Modifying the combination of endpoints,
- Adaptions of the study design,
- Changing the termination and continuing criteria,
- Changing the randomization

An adaptive trial design is also useful in cases where the mechanism of action of a substance is not fully understood or where a predictive marker to determine the treatment response is not available at the start of the clinical trial.

This means that many complex study designs (such as platform, umbrella and basket trials) also contain elements of adaptive trials. The purpose of such adaptive trial designs is identifying potentially promising new treatment approaches quickly, to implement them rapidly and to recognize futility as early as possible to be able to terminate less effective approaches.

“Umbrella Trials”

Umbrella trials (see Figure 1) investigate multiple biologically rational, drug-based treatments for a single disease, e. g. breast cancer or lung cancer compared to a unified control group. Samples of tumor tissue are screened for genomic or proteomic biomarkers and patients are subsequently assigned to different

treatment arms according to the presence or absence of these biomarkers (e.g. PD-L1, MSI, ALK, or HER2).

They frequently contain adaptive elements such as optional opening and closing of sub-studies/treatment arms where the decision is based on findings obtained during the trial on the effects of the investigational product on the molecular target. Furthermore, new biomarkers can be added to the trial protocol in order to treat patients in a more targeted fashion on the molecular basis of their disease.

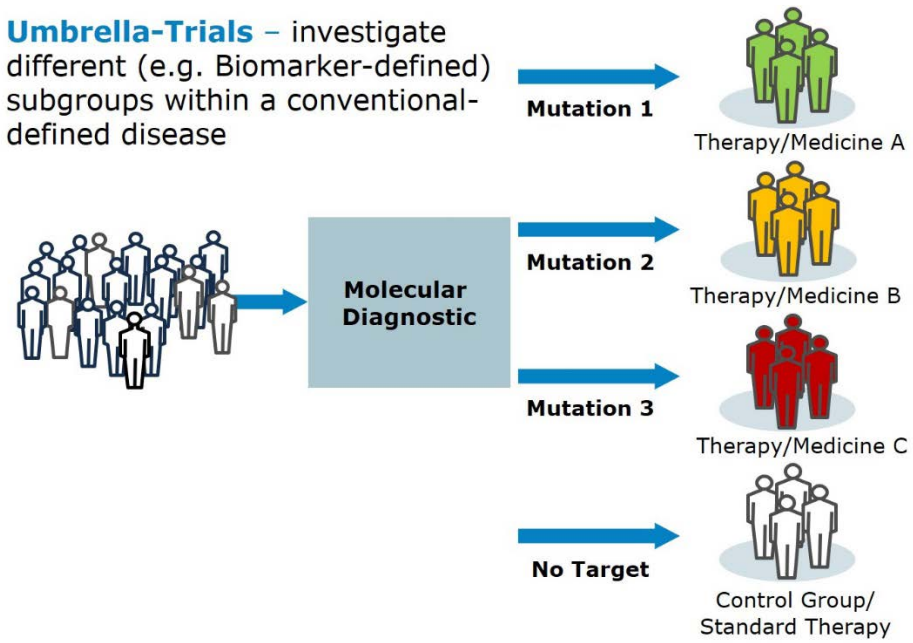

Figure 1: Approach of umbrella trials

The major advantage of umbrella trials resides in the following: Not only are patients with rare molecular subtypes identified (screened for multiple molecular variations) but the corresponding target treatments can be tested in the context of a clinical trial with a common control group in one unified clinical trial program. What is important is that molecular diagnostics are carried out in a timely manner using validated tests and that diagnostics and treatment physicians cooperate closely.

The importance of umbrella designs rests in the fact that they enable to characterize the patients tumor on a molecular basis and to assign the patient to a predefined molecular subtype. The molecular screening for subtypes can be conducted in a comprehensive way and may avoid multiple screening of patients for a single experimental treatment. The individual therapies can then be investigated in individual study arms or after an overarching screening trial as independent sub-studies.

"Basket Trials"

Basket trials (see Figure 2) are conducted to investigate single target treatments in patients with different diseases or disease types, e.g. lung cancer, colorectal cancer and skin cancer. For this approach it is required that the cancer types under study share one common biomarker (such as PD-L1, MSI, ALK or ROS) that promotes tumor growth.

Once the patients have been screened for the presence of a biomarker the positive ones are enrolled in the clinical trial. Adaptive approaches are possible in this scenario, too and other organ systems that exhibit this specific biomarker can be added to the protocol. Also, in the presence of new scientific findings regarding relevant tumor markers, further marker-based populations can be supplemented.

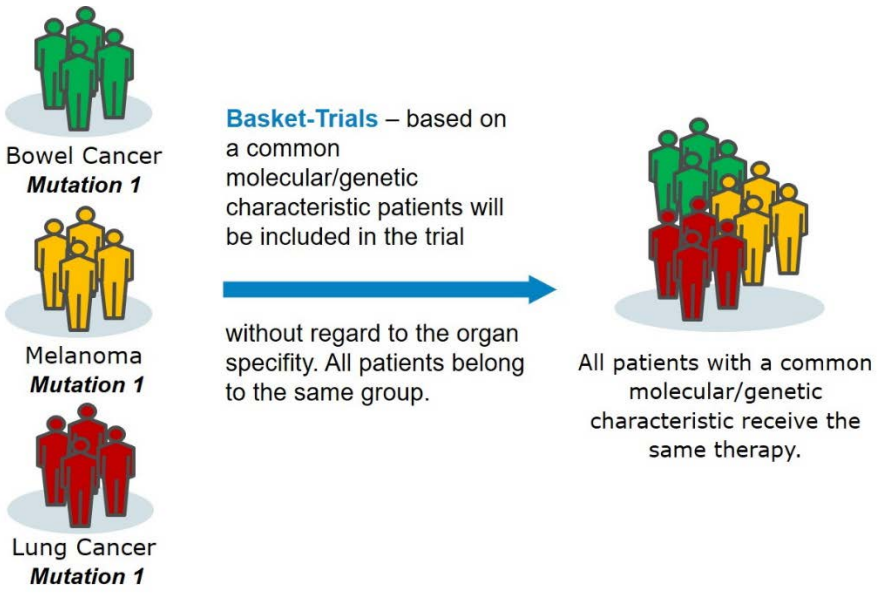

Figure 2: Approach of Basket trials

Experience has shown that treatment responses can vary greatly at times despite the patients bearing e. g. an identical mutation. In this scenario, diagnostic tests have to be carried out using validated diagnostic assays. As far as marketing authorizations (and the early benefit assessment) are concerned, it is important to bear in mind that different types of standard of care may have been established as comparator treatments for different tumor entities. The importance of Basket studies is that they allow to provide a more precise evaluation of treatment effects in different situations.

"Platform Trials"

In Platform trials (see Figure 3), multiple experimental targeted treatments are evaluated against each other in a single disease entity by comparison with a joint control group and under a master protocol. The patients are assigned to different treatment arms of the trial according to a predetermined decision algorithm. During platform trials changes are being made repeatedly as the trial progresses. For this reason, Platform trials are suitable specially for indications with short innovation cycles and decreasing target populations.

In theory, platform trials can be designed without fixing a specific timeframe because, in principle, new standard treatments (which evolved to this stage during the study) are emerging continuously and platform trials are able to accommodate such new developments during the conduct of the trial.

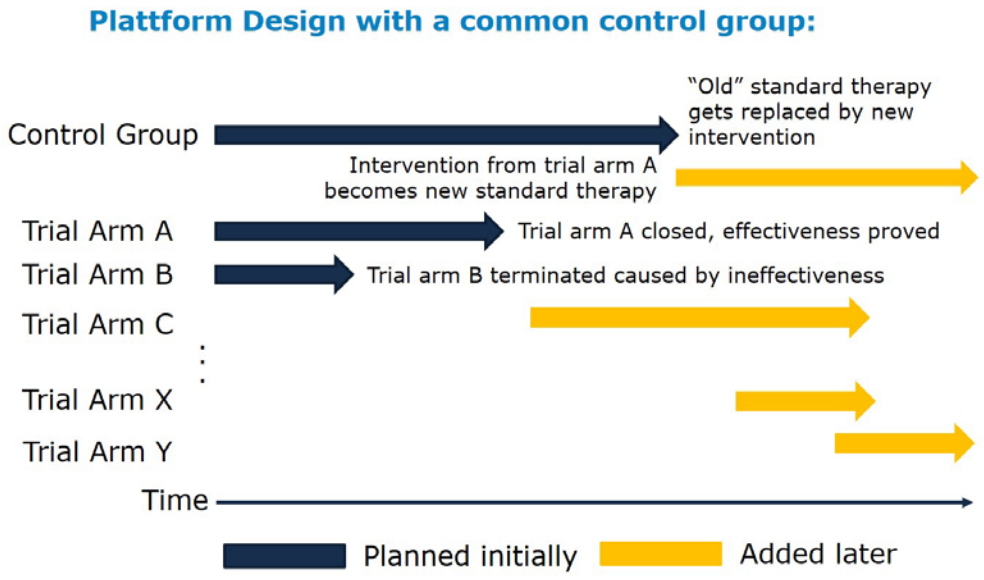

Figure 3: Approach of Platform trials

In the underlying master protocol of a platform trial the criteria for adding and closing individual treatment arms are defined upfront. The statistical methodology that is being used can provide for randomized treatment assignment, use of joint control patient groups and sequential analysis; it can also provide for the option of early closure of treatment arms in case of success or futility or adding new treatment arms, respectively.

C) The Perspective of the vfa

Classical study designs – such as randomized clinical trials – are currently pushed to their limits and fail to meet all the requirements of rapidly translating basic research into applied clinical practice with the aim to fulfil the medical need of patients as fast as possible. In addition, advances in research raise new questions in drug development that also require new approaches. Therefore, RCTs will increasingly be complemented by more flexible trial designs that are more efficient, especially in operational terms. These new adaptive approaches are of prime importance for advancing progress in medical science. At the same time, it must be ensured that these trials provide valid and robust results. This is of particular importance, since many current statistical methods can only partially compensate for the additionally generated distortions.

First steps for a wide-ranging discussion of the topic have already been taken, see article by Keller-Stanislawski *et al.* in Bulletin zur Arzneimittelsicherheit; edition June 2017: http://www.bfarm.de/SharedDocs/Downloads/DE/Arzneimittel/Pharmakovigilanz/Bulletin/2017/2-2017.pdf?__blob=publicationFile&v=6

In the opinion of the vfa the following criteria should be applied when planning and implementing complex trial designs.

Prospective Precise Decision Criteria

The trial protocol must prospectively define clear decision criteria that enable investigators to decide in each case which changes are permitted/required under the trial protocol. These definitions are important pillars for therapy critical decisions. Therefore, they must have been assessed and approved by the federal competent authorities and the ethics committees when the trial protocol is submitted to them. But on the other hand, flexible changes in the study design must remain possible especially for explorative trials.

The protocol should contain a transparent decision tree for biomarkers explaining what treatment arm patients should be assigned to during the clinical trial, particularly if their tumor e. g. exhibits several biomarkers in parallel. To discuss these decision definitions an intensive dialogue with the medical societies is required. Once patients have been assigned to a treatment arm, clear criteria are to be defined in what circumstances patients should switch to another arm of the trial or terminate the defined trial therapy (while joining the survival-follow-up-mode). This decision must always be taken together with the patient. Such a change can also get refused by the patient and consequently the patient would drop out of the active trial participation (see below). These independent decision criteria for a patient's trial participation of course have to be respected.

Complex Study Designs are of Prime Importance for the Explorative Trial Phase

Submissions with complex study designs that are basically clinical trial programs comprising phases I to III or seamless transitions from one phase to the next one have not been acceptable to the authorities and ethics committees and were rejected by these institutions in the past.

In the view of the vfa, it stands to reason that a clear distinction between exploratory phases (I-II) and confirmatory phases (II-III) must be preserved. It is also clear that complex trial design's focus is the exploratory trial phase. The sponsor of a clinical trial should, however, be obliged to set out the reasons in the study protocol as to why a particular approach was chosen in order to enable the regulatory authorities and ethics committees to appraise the selected approach formally. Dramatic effects at the beginning of a phase I trial represent special cases. In these cases, it has to be assessed how this therapy can be made available for medical practice and how it can be further supplemented with study data.

Referring to phase I and phase II studies it's the vfa's position that adaptive changes including those caused by external factors (e.g. new findings in basic research) can be helpful to promote the development of new medicines and enable patients a fast access to new treatments. It would be desirable for changes to be acceptable in this case without a substantial amendment being required by federal authorities and/or ethics committees, as long as change criteria are pre-specified in detail. The same would be useful for multiphase trials if staging criteria are clearly prespecified and can be comprehensively reviewed and approved by federal authorities and ethics committees.

In contrast, pure confirmatory phase III trials as RCTs should contain a clear predefined hypothesis and their design should not be adaptive. However, changes in the statistical analysis plan (SAP) should be possible as long as it is ensured that these changes don't get initiated by study results or external insights.

Avoiding Skewed Statistical Results (bias)

One important aspect particularly emphasized regarding complex trial designs by both regulatory authorities and ethics committees is the risk that effect sizes are over- or underestimated due to systematic errors when observing, recording, analyzing and reporting results (bias). To prevent this from happening, the protocol of the trial must contain a description of all potential bias factors as well as all procedures that will be put into place to avoid the occurrence of a bias (e.g. sensitive analyses) or, at least, to identify a potential bias by means of quality assurance procedures. Furthermore, the consequences of any identified bias and how to handle the data

affected must be clearly defined in the trial protocol. This is an iterative process and it is recommended to supplement the trial documentation in the case of new findings, also if they result from other studies

Clear Perception Required Regarding end of trial

Another concern from the view of the regulatory authorities and ethics committees with complex study designs, especially Platform trials is that the number of targets and, following from that, treatment arms are not always defined from the very beginning. This means that, in theory, a clinical trial could run indefinitely *("ad infinitum"*), because new targets/investigational products can be added, and treatment arms can be closed or newly opened while the study is ongoing.

This type of approach may be problematic for various reasons, because legal reporting requirements and specific quality assurance procedures for clinical trials etc. only come into effect after the completion of the trial. Therefore, the protocol should define a clearly identifiable end of the clinical trial or these procedures have to be done during the ongoing clinical trial. In case that appropriate reporting obligations/audits/inspections for the individual trial substances resp. studies are secured, trials with open end might be acceptable.

It would be desirable to have a clear statement how the reporting obligations and requirements for the individual treatment arms/sub-studies will be fulfilled. So, it would be useful e.g. to submit data memos/reports after completion of treatment arms or annual interim-reports for every target/treatment arm. A common position of sponsors, clinical scientists, Data Monitoring Committees (DMC), regulatory authorities and ethics committees should be found and defined.

Precise Role for an Independent DMC

Decision criteria for implementing changes in an ongoing clinical trial should not be fully evaluated by the sponsor alone. External bodies called Data Monitoring Committee (DMC) or Data Safety Monitoring Board (DSMB) or IDMC (Independent Data Monitoring Committee) should play a decisive role when critical treatment decisions need to be taken. The DMC has an important function in an ongoing trial, e.g. to assess achieved interim results, to influence the course of the trial and to direct decisions concerning the adaptions of study design/the SAP. For review by these committees, the trial protocol needs to prospectively define clear decision criteria that are decisive for the committee's actions.

It is also important to ensure the independence of these committees and their decisions taken. For the reasons mentioned, precise guidelines for the membership of persons in DMCs are essential to be defined and these guidelines should be submitted to the regulatory authorities and ethics committees. This will allow these bodies

to assess the proposed composition of the committee and ensure and verify its independence.

Furthermore, the interactions within the DMC must be subject to clear rules and the DMC Charter should define roles and responsibilities, the type of data that will be assessed and the type of data on which decisions are based (e.g. blinded vs. unblinded data). This also applies to the cooperation with the authorities/ethics committees that must be clearly defined in the DMC Charter. This is important, because in case of severe safety issues the DMC must cooperate with the competent regulatory authority and the trial sponsor and be in a position to provide transparent information on the background and on the decisions that were taken on the basis of prespecified decision criteria.

Involving the Study Participants

Another important point with respect to adaptive designs is that study participants must always be fully informed about a clinical trial. Importantly, complex trial designs should always be fully explained, and the benefits and risks explicitly mentioned to allow potential study participants to make an informed decision about taking part in the trial. It must be acknowledged that in the case of complex trials the informed consent discussion poses particular challenges to the investigator involved in the study. For the above-mentioned reasons, sponsors of clinical trials should provide information and educational material that explains the study design in the simplest terms possible and explicitly mentions the associated benefits and risks. When adding or closing treatment arms, all patients (study participants and patients to be enrolled) should be fully informed to ensure understanding of the changes to the study design and to allow patients to withdraw from the clinical trial (and to switch in a follow-up-mode), if they wish so.

But it is essential that this doesn't results in an overload of information for the patients. All information should therefore be focused on relevant aspects for the treatment arms that affect or are relevant to the patient(s) concerned. Therefore, the definition of suitable approaches between the trial sponsor and in particular, the ethics committees is an important prerequisite here.

Discussion about Reimbursement with the Relevant Payers

For national/international HTA bodies randomized clinical trials (RCT) are the gold standard to assess clinical effects of causal benefits and risks in a scientific way. The HTA bodies have to explicitly recognize that many variations of RCT designs are being used to meaningfully address legitimate critical research questions and to meet the challenges of dynamic clinical research contexts, including complex study designs. These designs can't get refused in general.

Consequently, therefore, a comprehensive dialogue with decision-makers on reimbursement is important. However, e. g. the IQWiG

– which plays an important role in the HTA process in Germany - has in the past formulated requirements for trial designs in the context of personalized medicine, which methodologically represent an ideal image, but which are not realistically feasible due to the required high number of patients and in some cases would not be ethically acceptable. It is therefore always important to keep an eye on the practical feasibility of clinical trials. Pragmatic solutions, especially when widely discussed and consensual, must also be acceptable for the HTA bodies for their added value assessments.

The discussion of study designs and requirements with the relevant stakeholders should include all aspects and players, particularly the HTA bodies, so that the results generated by these complex clinical trials get comprehensively acknowledged and accepted in approval and HTA processes.

Discussion with all Stakeholders

In general, an intensive dialogue between all stakeholders is important, because it can result in a workable and accepted agreement for all involved parties. The vfa is open for such discussions but would like to stress the relevance of taking an international perspective in this dialogue and not to discuss this topic only at a national level.

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