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Stakeholder Perspectives on Randomized Clinical Trials for Children With Poor-Prognosis Cancers

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Abstract

IMPORTANCE In poor-prognosis children's cancers, new therapies may carry fresh hope for patients and parents. However, there is an absolute requirement for any new therapy to be properly evaluated to fulfill scientific, regulatory, and reimbursement requirements. Randomized clinical trials (RCTs) are considered the gold standard, but no consensus exists on how and when they should be deployed to best meet the needs of all stakeholders.

OBJECTIVE To conduct a multistakeholder meeting to foster a greater shared understanding of perspectives regarding RCTs of new therapies for children with poor-prognosis cancers and develop consensus recommendations on when and how they should be used.

EVIDENCE REVIEW During October 2022 and April 2023, 2 structured workshops were convened, bringing together individuals representing the perspectives of patient advocates and academic clinician-researchers, regulators, and health technology assessment bodies. A premeeting briefing document was prepared and circulated to all attendees. During the workshops, selected attendees presented on behalf of each stakeholder group, focused topic discussions were conducted, and each meeting concluded by agreeing on a consensus set of recommendations. Meeting organizers drafted meeting summary reports that were circulated to all attendees, who commented on and revised them as a group to produce final recommendations from the workshops.

FINDINGS Though the workshops did not reconcile all stakeholder differences, sufficient areas of agreement enabled a set of conclusions to be drawn, resulting in 8 consensus recommendations: (1) drug development strategies for new therapies, including the role of RCTs, should be established at the time of first-in-child studies; (2) engagement with regulators and health technology assessment bodies about RCT design is crucial; (3) involvement of patient advocates is necessary to ensure that an RCT is patient focused; (4) timing of an RCT is critical to preserve clinical equipoise; (5) use of crossover in an RCT can be of benefit, but with important caveats; (6) end point maturity and overall survival in an RCT may be important for regulatory and health technology assessment approvals; (7) in the absence of an RCT, contemporaneous control cohorts are preferred over historical control cohorts; and (8) quality of life should be captured in all prospective RCTs.

CONCLUSIONS AND RELEVANCE The agreed-upon workshop conclusions provide a basis for key considerations while undertaking future drug development activities for children with poor-prognosis cancers, ensuring that the needs and perspectives of all stakeholders are factored in from the outset.

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Introduction

To maximize their contribution to pediatric oncology drug development, patient advocates must blend lived experience with acquired knowledge of a complex ecosystem. Under the auspices of Childhood Cancer International Europe and supported by a European Union (EU) operating grant, patient advocates organized 2 multistakeholder workshops on randomized clinical trials (RCTs) in poor-prognosis children's cancers. The purpose was to share perspectives on the role of such trials with the aim of fostering a greater understanding of when and how to conduct RCTs for the maximum benefit of current and future children.

Motivation for the workshops stemmed from a breakout session on RCTs at the ACCELERATE Conference 2022,[1,2] discussions during ACCELERATE pediatric strategy forums on chimeric antigen receptor T cells[3] and multitargeted kinase inhibitors in bone sarcomas,[4] and the rEECur phase III trial for recurrent and primary refractory Ewing sarcoma presented at the 2022 American Society of Clinical Oncology Annual Meeting.[5,6]

Methods

In October 2022 and April 2023, 2 workshops were held to bring together stakeholder groups comprising patient advocates and academic researchers from Europe and North America, regulators from the European Medicines Agency and US Food and Drug Administration, and a health technology assessment (HTA) perspective from the Norwegian Medical Products Agency. Parents with lived experience of having a child with cancer were the predominant advocate voice. Ethics committee approval was not sought for the project as it was considered out of scope for such a review, per the Common Rule.

In the first workshop, each stakeholder group shared its perspectives based on 2 case study RCTs presented to explore the investigator experience: the rEECur phase III trial for recurrent and primary refractory Ewing sarcoma[5,6] and OLIE, a phase II trial for relapsed and refractory osteosarcoma.[7,8] Following this exercise, 2 focused discussions were held. The first discussion focused on the hope and expectation of benefit from new therapies vs a competing and compelling need to generate robust scientific evidence. The second discussion focused on the use of RCTs in the context of an overarching drug development strategy, including the need to satisfy regulatory and reimbursement requirements.

The second workshop comprised an educational session on clinical trial designs, biostatistical methodologies, and end points, followed by a discussion on designing trials to balance hope, scientific rigor, and impact for current and future patients. The final session of each workshop gathered the discussion and debate into a set of agreed-upon conclusions.

Perspectives and Discussion

There are divergent views across stakeholder groups due to their different perspectives and priorities and the mandates under which they operate. Heterogeneity also exists within stakeholder groups. The **Figure** highlights aspects relevant to each stakeholder group. Use of language and context was identified as important in interactions among stakeholders. For instance, small patient populations and poor prognosis were terms used frequently but without a common definition of their meaning. Standardization of terminology may warrant further exploration in the future.

Parents and families view clinical trials as a way of contributing to research, but even more critically, as providing an opportunity to access new and experimental therapies with the hope of individual benefit regardless of the research purpose.[9,10] In the context of an RCT in a poor-prognosis setting, there can be a prevailing sense of needing to beat the odds. The possibility that a new but unproven therapy could be better drives parents' instincts to favor that therapy over an established treatment with limited effectiveness and even more so when a new therapy is being added to an

established treatment in an experimental arm.[9] The worse the prognosis, the greater the hope that a new therapy will be better and the stronger the parents' desire for their child to receive it. The more promising a new therapy appears to be, through early results published or presented at meetings or off-label or expanded access use reported anecdotally, the more such hope is fueled.

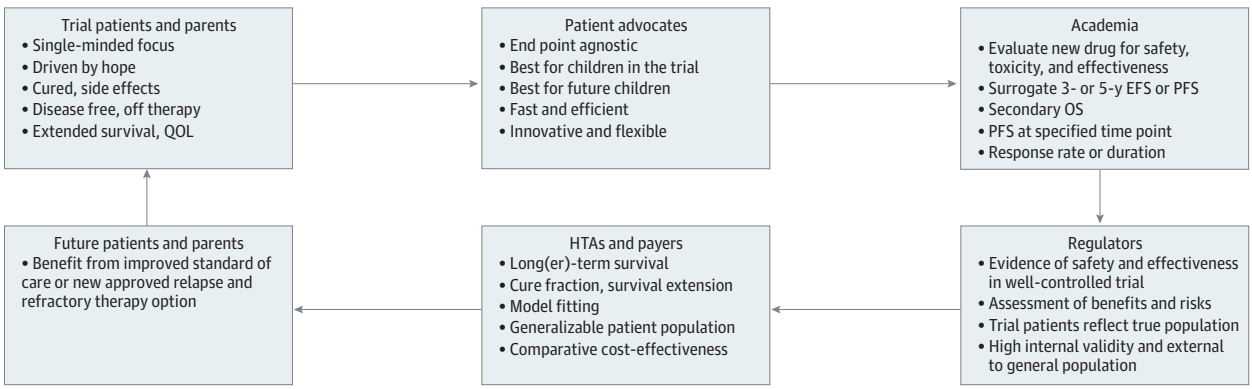
Patient advocates are motivated by wanting the best for children today and the best for children in the future, which may create internal conflict. On the one hand, many advocates have lived experience of the instincts of parents whose focus is predominantly on their own children. On the other, they acknowledge the need for scientific integrity and successful navigation of regulatory and reimbursement systems if future children are to benefit. These competing forces manifest in a call for innovation in trial design and speed and efficiency in trial execution within a cohesive drug development and overarching treatment strategy.

Academic investigators conduct clinical trials to rigorously evaluate the safety, tolerability, and effectiveness of new anticancer agents and treatment modalities, with the ultimate goal of improving standard of care for patients. Randomized clinical trials are deemed the gold standard.[11] When patient numbers are small, an RCT using relaxed statistical error rates is preferred over a single-arm trial with a historical control arm, an approach supported by regulators.[12] An RCT in relapse and refractory disease could be practice changing in that setting, an intermediate step toward moving to crucially important frontline trials, or both. Academic researchers caution that new therapies may ultimately be worse in terms of survival, toxicity, or both.[13] Promise in early-phase trials may not hold in a well-controlled and suitably powered RCT.[13,14]

An important concept to emerge was that of clinician-researcher hope. Clinicians professionally invested in developing a new therapy do so in the hope that the therapy will improve outcomes for patients, and they may become emotionally invested in this work. Promising signals in early results may intensify their hope.

There is a need to preserve clinical equipoise in RCTs for both families and clinicians that requires conducting the right trial in the right patient population at the right time and timely progression of development. While there must be some indication of potential improvement in survival and/or quality of survival from a new therapy before an RCT is proposed, the greater the expectation of benefit, the more some might view randomization as morally and ethically problematic. Insufficient buy-in from families and clinicians may compromise recruitment, threatening the internal and external validity of a trial and lengthening the time it takes to complete. If a new therapy is available through other routes (eg, off label), it may be challenging for an RCT to be successfully conducted. Innovations in the design of RCTs, such as crossover and/or unequal

Figure. Stakeholder Perspectives and Key Considerations



While each stakeholder group in turn has its own perspectives and requirements, navigating through all enables an effective new therapy being evaluated in clinical trials to result in improved standard of care. EFS indicates event-free survival; HTA, health technology assessment; OS, overall survival; PFS, progression-free survival; QOL, quality of life.

randomization ratios, may make trials more attractive to families while seeking to maintain necessary scientific robustness.

Regulatory authorities require evidence of safety and efficacy within 1 or more well-controlled trials to assess benefits and risks as part of a marketing authorization application. While RCTs are widely considered to provide the highest quality evidence to support an approval,[15] regulators may accept single-arm trials in a context-specific manner,[16-18] and there is a continual evolution of regulatory science.[19]

Health technology assessments are required across Europe and elsewhere for reimbursement of a new therapy by national health care systems,[20] and these involve analysis of comparative effectiveness relative to cost. The HTA considers 3 broad areas when assessing a new therapy: (1) end point maturity, ie, does the new therapy perform the same beyond the trial; (2) comparative clinical effectiveness and cost-effectiveness, ie, how does the new therapy perform against what is already available, including cost; and (3) quality of life, ie, how does the patient feel, and what is the burden of treatment? While single-arm trials are problematic for HTAs given the need for comparative effectiveness, use of a contemporaneous external control arm is preferable to a historical control arm. Hybrid designs that leverage recent patients as an external control cohort to augment a randomized control arm, thus requiring fewer patients to be randomized to receive standard therapy, may also provide a pragmatic way forward.

The choice of end point in an RCT, for instance event-free survival (EFS) or progression-free survival (PFS), is another key consideration. Most clinical trials in pediatric oncology use EFS, PFS, or similar, but overall survival (OS) may be important to regulators and HTA bodies. Use of predictive biomarkers may play an important role in reimbursement approvals, identifying those patients for whom a new therapy is most likely to work, thereby sparing it being given (or paid for and given) to all patients, including many who do not benefit. Quality of life is a crucial determinant of relative benefit beyond survival end points and something to which HTA bodies ascribe value.

The HTA body's role of assessing value for money in relation to health care spending by evaluating cost-effectiveness and affordability may inevitably place them at odds with parents for whom no price can be placed on their child's life. Moreover, heterogeneity across HTAs means that the same trial with the same data for the same indication may be assessed differently, including by member states within the scope of an EU marketing authorization.[21] Collaboration among HTA bodies in Europe has been facilitated by the EUnetHTA 21 Consortium, which no longer exists.[22] Preparations for implementation of the new EU HTA Regulation continue.[23]

Box. Recommendations for Randomized Clinical Trials of New Therapies for Children With Poor-Prognosis Cancers

1. The drug development strategy for a new therapy, and the potential future role of randomized clinical trials (RCTs) within it, should be clearly set out when planning first-in-child studies.
2. Early and meaningful engagement with regulators and health technology assessment bodies about the design of a clinical trial is crucial to ensure that it is fit for future purpose.
3. Substantive early engagement of patient advocates in the design of an RCT is important to ensure that it is patient focused. Clinical trial design meetings should include expert patient partners starting from the first discussions.
4. Timing of an RCT is critical to preserve clinical equipoise. There is a need to move rapidly to conduct the right trial at the right time.
5. Use of crossover in an RCT may be a win-win for patients and investigators, but there are important caveats.
6. Event-free survival and progression-free survival are important primary end points, but end point maturity and overall survival may be important for regulatory and health technology assessment approvals.
7. In the absence of an RCT, contemporaneous control cohorts are preferable to the use of historical control cohorts.
8. Quality of life is an important determinant of benefit and should be captured in all prospective RCTs.

Results

While the workshops did not harmonize all stakeholder differences, there were areas of agreement that enabled a set of conclusions to be drawn. These are highlighted in the **Box** and discussed in greater detail below.

Having an Overarching Drug Development Strategy

An overarching drug development strategy for a new therapy, and the potential future role of RCTs within it, should be clearly set out when planning first-in-child studies. In Europe, a stepwise pediatric investigation plan may underpin this strategy to provide complete lifecycle support.[24,25]

Early Involvement of Regulators and HTAs

There should be early meaningful engagement with regulators and HTA bodies to ensure that requirements leading to future authorizations are met if trial results are positive. Discussions between industry and regulators regarding drug development plans and prospective clinical trials should necessarily also include both academia and advocates.

Involvement of Patient Advocates

There should be substantive patient advocate involvement alongside academic investigators early in the design of an RCT to ensure that the study is suitably patient focused. A trial must be attractive to patients and families to recruit efficiently and minimize the potential impact of poor enrollment and nonadherence. A consensus from academia and advocates (endorsed by regulators) was to aim for the first design meeting for a clinical trial to include expert patient partners.

Equipoise and Timing of RCTs

Rapid implementation of an RCT is crucial to preserve the buy-in of patients, parents, and clinicians, without which such a trial cannot be successfully completed. Judgments on clinical equipoise may vary across individuals, but if there is a general sense that it no longer holds, then a trial may appear unethical. The process of moving a new therapy through relapse trials and into the frontline setting, where it can have the greatest benefit, must be performed as efficiently as possible. For equipoise to hold, academic researchers must not unduly fuel hope in an unproven experimental therapy. Ultimately, a new therapy not properly evaluated may never be approved or reimbursed and, hence, fail to become standard of care, regardless of the impact it might have had.

Crossover Designs and End Points

The use of crossover designs in RCTs in poor-prognosis cancers may represent a win-win for patients and investigators. However, there are important caveats, such as the need for care around disease reassessment and scheduling to prevent premature crossover that could introduce bias. The use of an early end point, such as EFS or PFS, in a crossover design may compromise evaluation of an OS end point, which may be problematic since OS is often an important end point for regulators and HTA bodies.[26] However, most patients receive additional therapies following disease progression regardless, and these too may have a similarly confounding effect. With OS generally regarded as the most clinically relevant end point for clinical trials in oncology, the appropriateness of any surrogate end point must be adequately demonstrated.

Maturity of End Points

For assessing comparative clinical effectiveness and cost-effectiveness, HTAs need maturity of end points and generalizability of results to a longer-term patient population. A strategy that addresses the time lag between the primary end point of an RCT and more mature outcome data required by regulators and HTAs may be required. For example, use of an early end point for an accelerated

approval and a subsequent mature or confirmatory end point for full approval may be part of the design.

Use of External Control Patient Populations

Randomized clinical trials with relaxed statistical error rates may be appropriate for small molecularly or clinically defined patient populations. However, in the absence of an RCT, use of a contemporaneous external control cohort should be considered ahead of a historical control cohort. Such a control group could comprise patients unable or unwilling to participate in a clinical trial who are instead treated with standard of care or physician preference, with their data appropriately collected.

Importance of Quality-of-Life Assessment

Quality of life and burden of treatment obtained through patient-reported outcomes are important determinants of relative benefit, not only survival. Accordingly, improving the design of clinical trials to routinely incorporate such measures and facilitate the collection of patient-reported outcomes is important.[27]

Conclusions

Improvements in cancer treatment for children have been made through slow and stepwise progress over the past 50 years.[28] The agreed-upon conclusions presented herein lay a foundation for key considerations regarding the future use of RCTs in drug development activities for children with poor-prognosis cancers. Their purpose is to ensure, to the greatest possible extent, that the needs and perspectives of all stakeholders are acknowledged and factored in from the outset. Although there were divergent views among workshop participants about the role, and indeed appropriateness, of RCTs in the context of a poor prognosis, stakeholders agreed that discussing issues and working together represents the best way to maximize future progress.

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