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Title page

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Key words: psychosocial studies, pediatric oncology, intervention studies, randomized controlled trials, recruitment, retention

Trial registration: this study is not a clinical trial.

What's Known

Performing RCTs is challenging, particularly in pediatric psychosocial research when both the child and parent are targeted. Recruitment and retention are common concerns. In pediatric oncology, there are few examples of successful recruitment and retention strategies in psychosocial care research.

What's New

Key strategies to collaborate constructively with healthcare professionals were outlined. Being flexible, training the research staff, alignment with the participant's situations and providing

consistency in contact between the research staff member and the families were considered as essential strategies.

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Abstract

Objective: In pediatric oncology there are few examples of successful recruitment and retention strategies in psychosocial care research. This study aims to summarize experiences, challenges, and strategies for conducting randomized controlled trials (RCTs) of psychosocial intervention studies among children with cancer and their parent(s).

Methods: We conducted a collective case study. To identify the cases, Pubmed and two trial registries were searched for ongoing and finished RCTs of psychosocial intervention studies for children with cancer and their parents. Online semi-structured expert interviews discussing recruitment and retention challenges and strategies were performed with principal investigators and research staff members of the identified cases.

Results: Nine studies were identified. Investigators and staff from seven studies participated, highlighting challenges and strategies within three major themes: eligibility, enrollment and retention. Regarding eligibility, collaborating constructively with healthcare professionals and involving them before the start of the study were essential. Being flexible, training the research staff, enabling alignment with the participants' situation, and providing consistency in contact between the research staff member and the families were important strategies for optimizing enrollment and retention. All studies followed a stepped process in recruitment.

Conclusion: Although recruitment and retention in some selected studies were successful, there is a paucity of evidence on experienced recruitment and retention challenges in pediatric psychosocial research and best practices on optimizing them. The strategies outlined in this study can help researchers optimize their protocol and trial-implementation, and contribute to better psychosocial care for children with cancer and their parents.

Abbreviations:

pACP – pediatric Advance Care Planning

RCT – Randomized controlled trial

SWAT - Study Within A Trial

INTRODUCTION

Randomized controlled trials (RCTs) are the optimal way to minimize bias and optimize inference when evaluating treatments, therapies, and innovation in healthcare[1]. However, performing RCTs is challenging, particularly in pediatric psychosocial research. Recruitment and retention are common concerns, in part because potential subjects may have pre-conceived notions about the interventions being studied (i.e., those that address mental health or communication of sensitive topics), and in part because these studies often involve substantial time commitments (i.e., for study procedures or questionnaires)[1,2]. Approximately half of these trials require extensions of time and/or budget to successfully recruit their target sample[1].

Previous studies in children with serious illnesses have explored recruitment and retention challenges[3,4]. In studies testing interventions for adolescents and young persons with chronic conditions, for example, participation may require directly identifying with their illness at a time when the subjects prefer otherwise. As a result, enrollment rates have ranged from 10 to 50%[3]. Similarly, psychosocial interventions may address topics that are sensitive to healthcare professionals and parents, raising challenges in the approach and enrollment for clinical trials[4]. Even when subjects do enroll, retaining them on these studies can be difficult due to the inherent burdens of study-participation; in a review of 40 clinical RCTs for parents and youth living with chronic illness, reported attrition rates were as high as 54%[5]. In pediatric oncology, there are few examples of successful recruitment and retention strategies in psychosocial care research[6]. Strategies such as medical director involvement in the recruitment group and information sessions for eligible families were ineffective in one study in a large children's cancer center[7]. In another study, a stepped process for recruitment was identified as an effective approach, where families were introduced to the study in a more person-centered way, spread over multiple contacts[6], and recruitment at

diagnosis, face to face, and with the use of short questionnaires yielded higher participation[8]. Although having a coordinator to monitor data collection across sites as a strategy to improve response rates lacked effectiveness[9], involvement of the clinical team in the contact strategy does seem to enhance retention[10]. However, due to the inadequacies of current reporting practices, judging the impact of different recruitment and retention strategies is challenging[11]. In general, there is a clear knowledge gap with regard to effective strategies aimed at recruitment[12].

To advance the conduct of psychosocial RCTs among children, we aimed to provide a detailed description of the experienced recruitment and retention challenges, and strategies to overcome them, from psychosocial intervention studies conducted among children with cancer and their parent(s).

METHODS

Design

We conducted a collective case study, selecting multiple cases to generate an in-depth, multi-faceted understanding of a complex issue in its real-life context[13], and to allow us to detect patterns in recruitment and retention challenges and strategies to overcome these across the different psychosocial intervention studies. Online semi-structured expert interviews were conducted with principal investigators and research staff members of a selection of recent or ongoing trials testing psychosocial interventions for children and/or adolescents with cancer and their parents.

Selection of cases

To identify our cases, we used an elaborate search on Pubmed **(Table 1)** and the ClinicialTrials.gov and ISRCTN.com trial registries in January 2022. Inclusion of studies was critically discussed with the core research team (ADV, KB, LD, JC, MK). Included cases (a)

involved interventions that have psychosocial components (defined as any intervention that emphasizes psychological, educational, or social factors, rather than solely biological factors)[14], (b) included children/adolescents with cancer (on treatment) up until 25 years old, (c) included at least one parent in the study, (d) were either finished or ongoing studies and (e) were individually randomized controlled trials without an active comparator **(Table 2).** This search allowed us to identify the principal investigators (PI) of these studies and to collect relevant recruitment- and retention-related information, which was used to learn about the study before the interviews and was processed in our topic lists. The PIs were contacted by email and were allowed to invite a maximum of two other research staff members they thought would be able to give in-depth information on recruitment and retention challenges and strategies.

In March 2022, the corresponding authors were invited per email for an online interview of approximately one hour. If they did not respond after a maximum of three reminders, we contacted them via ResearchGate or contacted one of the other authors. Participants were offered a reimbursement of 60 euros for their time.

Data collection

The interviews took place in March and April 2022, via Zoom, using a self-developed topic list **(see Additional File 1).** Domains represented in the interviews were: 1) Actions before the study start; 2) Screening for eligibility; 3) Enrollment; 4) Attrition; 5) Encountered challenges; 6) Additional strategies to enhance recruitment; 7) Advice to other researchers. To prepare and tailor each interview, we asked the participants to send us documents (such as information letters and protocols) they used regarding all aspects of recruitment and retention.

Analysis

All interviews were audio recorded and transcribed verbatim. The principal author analyzed all interviews, using a combination of deductive and inductive thematic analysis[15].

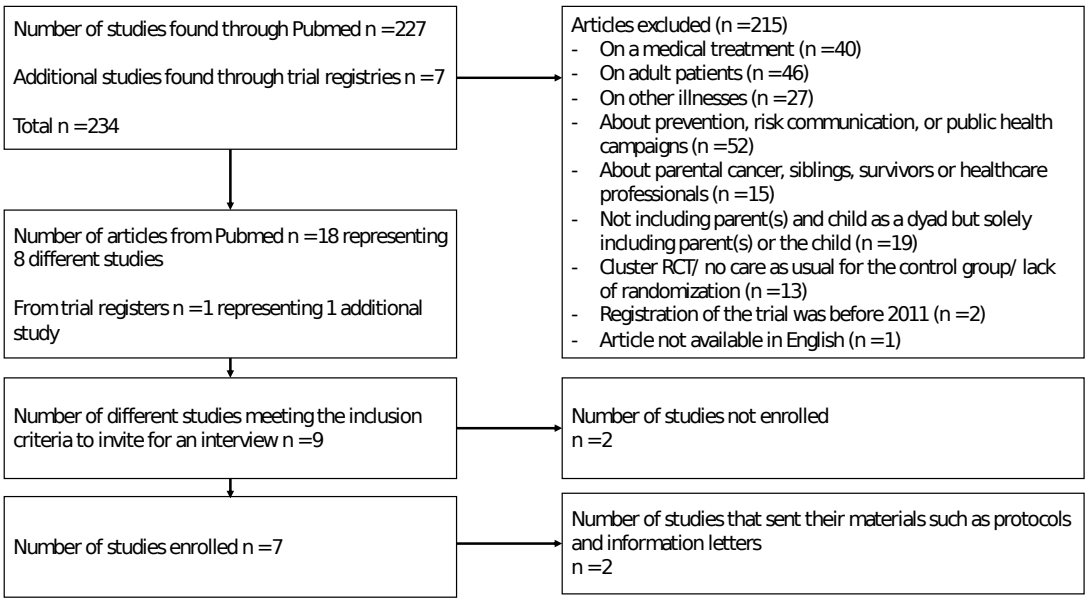
Transcripts were read line by line and data were coded into an a priori framework of the seven domains of the topic list (deductive component). Data within each category was then coded in order to create sub-categories (inductive component). NVivo version 20 software assisted in data organization. Main findings were discussed with the research team to enhance reliability of interpretations.

RESULTS

3.1. Selection of cases

In total, 234 studies were identified. Of these, nine studies met the inclusion criteria **(see Fig. 1**). The authors of one study[16] declined participation in the interview and we could not reach the authors of one other study[17]. The remaining 7 studies were included (**Table 3**).

Fig. 1. Flow chart of the selection process



3.2. Results from the interviews

The interviews lasted between 59 and 83 minutes. We identified challenges related to three major themes: eligibility, enrollment and retention (discussed below) - as well as participant-suggested strategies to address these challenges **(**listed in **Table 4)** and general considerations for future investigation including illustrating quotes **(Table 5).**

Eligibility

We identified three challenges related to eligibility screening. First, respondents indicated that determining eligibility criteria could be challenging because they needed to balance feasibility of enrollment within a certain timeframe with the need to target experiences within specific, small populations of youth. A psychosocial intervention is often developed and tested for a specific age group with a corresponding cognitive development. This creates ***a tension between broadening eligibility in view of numbers and the target group specificity in view of the intervention*.** Some respondents indicated they changed certain criteria, such as the age of children or types of cancer, because they noticed interest in that group or because they saw this increased the feasibility of recruiting a sufficient number of participants within their timeframe.

Second***, gatekeeping by healthcare professionals*** was often mentioned as a barrier. Respondents believe this behavior was usually well-intentioned; clinicians hoped to protect families from potential stressors associated with the study-topics. Although some respondents regarded healthcare professionals watching out for the potential risks of participating in a study as a strength because they know more about the family's illness trajectory and burden, this sometimes led to disagreement between data collectors and healthcare professionals concerning the family's eligibility. Studies depending on healthcare professionals for introducing the study experienced additional challenges in maintaining awareness among the

professionals about the study and their crucial task of checking families' eligibility and introducing the study to eligible participants.

Third, as childhood cancer qualifies as a rare disease [18], ***multiple sites must often be involved to increase the pool of eligible participants,*** which entailed extra challenges such as a lack of control over the approach and the procedures in the various sites. Moreover, it took a lot of time to arrange legal contracts to be able to share protected health information among the different sites, with some legal departments being extra cautious because the research involved children with cancer. In the case of the BOOST pACP study, additional legal parties had to be involved, which required extra time.

Enrollment

Seven themes related to enrollment challenges were identified. Enrollment rates varied depending on the site and research assistant. Recruitment for psychosocial studies in this target group usually takes a long time. Within the long recruitment period, ***staff turnover within the research team*** was inevitable, which created difficulties regarding finding new motivated and flexible members. Some respondents noticed that the enrollment rate would drop after hiring new research assistants. Finding and training suitable new staff took time and resources. New research staff members, in particular, found it often difficult to interact with families going through these difficult experiences, because they did not want to add to the family's burden. Consequently, they were extremely careful introducing the study, which sometimes negatively impacted enrollment rates.

Willingness to participate was often overestimated by the research team. Through surveys, several respondents had tried to gain insight into families' reasons for not participating in the study, but the response rate on these surveys was low. The insights obtained revealed that the families' reasons for refusing to participate were: feeling overwhelmed having to combine

their family life with regular visits to the hospital; perceiving the health status of the child as not good enough; or simply not having the mental headspace to commit to something extra, regardless of the study. The children's most mentioned reason for not participating was wanting to feel normal without being preoccupied with being sick.

Respondents acknowledged that ***children or adolescents with cancer and their parents are an overburdened research population.*** Our respondents mentioned that there were often competing studies in the same target group during the time of recruitment. One study (FAMOS) could not include families of children between 6 – 18 years for that reason, and were thus constricted to include only a part of their original target group (0 – 18 years). Medical studies are often prioritized: for example, a child eligible for the BOOST study said she had already participated in a medical trial, preferring that over a study with psychosocial components.

According to our respondents, another factor potentially influencing enrollment rates was that ***families are randomized into groups.*** Families did not always understand the concept of randomization and did not fully know what they were signing up to. Some families also had a clear preference for one of the groups.

The dyadic nature of the enrollment and needing both the parent(s) and the child to be willing to participate, complicated this kind of research. Encountering both the child and one of the parents in the same room at the moment of introduction in the hospital often took several visits. Parents regularly assumed that their child did not want to participate, or they wanted to protect them from potential harm. Requiring the signatures of both caregivers took additional time, because they were usually not present at the hospital at the same time and they had to discuss participation at home.

Finding an appropriate time to introduce the study to the family was experienced as an important part of building up contact with the families. However, this was also seen as a

prominent challenge because, as many families were in the hospital to receive news or heavy treatment, it was difficult to estimate the burden at that moment.

Lastly, ***the COVID-19 pandemic*** was detrimental to many ongoing studies, because it further negatively influenced families' willingness to participate. Moreover, some respondents felt that in-person recruitment worked better (addressing families and being present in the wards), which was not possible during the lockdown periods.

Retention

Two themes in retention challenges were identified. All respondents faced ***non-response and drop-out*** in their studies. In some studies, the drop-out rate was higher in the intervention group compared to the control group. Respondents hypothesized that this could be due to the intervention taking a lot of time or not being sufficiently user-friendly. The respondents from studies in which drop-out was higher in the control group speculated that this could be caused by them being contacted and engaged less often throughout the study period or by them being less motivated because they did not receive an intervention in return.

Another challenge impacting retention was ***keeping per-protocol timelines versus required flexibility*****. Once families had been enrolled,** it was challenging to follow the protocol and keep to the predefined time window, especially when psychosocial interventions consisted of several intervention sessions and questionnaires. Some children were admitted to the intensive care unit (ICU) during the study period, or sessions needed to be rescheduled because parents were exhausted or had other obligations, which impacted the planning of the follow-up sessions. Therefore, the risk of families having to drop-out is increased and a certain amount of flexibility is required.

General challenges experienced by the respondents

Three overarching challenges were elaborated on during the interviews. For an indication of how many recruitment sites are required and how much time is needed to enroll the target number of participants, most respondents performed a pilot test. However, in some cases – due to different circumstances in the larger study - ***the numbers in the pilot study were vastly different from the numbers eventually enrolled in the larger scale trial***.

In addition, ***some studies had to pause enrollment because another recruitment strategy they wanted to implement was not included in their initial, IRB-approved, protocol.***

Lastly, ***ending up with enough recruitment sites willing and able to participate in the study*** was mentioned to be challenging. Therefore, one respondent recruited via social media (Facebook) instead. Although this eventually worked well after gaining expertise in creating and running an advertising campaign, the respondent argued that this is not applicable to every population and success is difficult to predict.

DISCUSSION

This collective case study gives an overview of the most commonly experienced recruitment and retention challenges, plus strategies to overcome them, while conducting RCTs of psychosocial intervention studies for children with cancer and their parents, sub-divided into three themes: eligibility, enrollment and retention. Although many studies were found on this target group, they mostly used different designs, such as pretest-posttest designs without a control group, cluster RCTs, or used an attention control group. Other studies we found stated that they did not randomize due to ethical and practical considerations. The limited number of studies meeting our inclusion criteria, may indicate that conducting individually randomized controlled trials without an active comparator in this field and target group is rare, possibly because it is very challenging.

All of the respondents followed a stepped process for recruitment, using a personalized approach, with several visits per family. Bradford et al. (2021)[6] estimated it takes an average of 98 min for an experienced research member to screen, approach and recruit one participant in a pediatric oncology setting, emphasizing the importance of training all research staff (involved in referral, data collection, and intervention) [19]. This training could entail ways to perform systematic screening of patient lists, thoughtful messaging to make the study relevant, and how to deal with flexible protocols to accommodate patients' needs[20]. Furthermore, communication with families in the pediatric oncology setting - and striking the balance between respectfully recognizing their burden without being too careful introducing the study - should be part of the training. As participants, including children and adolescents, reported benefits including the opportunity to talk, be altruistic, reflect, have a safe space, gain understanding or perspective, and express emotions [21], potential advantages of these kinds of studies may be presented to eligible families also. More transparency on the content

of these trainings from trials in this setting would be of added value for researchers to use as a reference.

One of the overarching recommendations from our respondents was to perform a pilot study prior to the larger scale trial. Testing feasibility and acceptability by conducting a pilot study is widely accepted as a great value, if not a necessity, for RCTs[22] as they can "*inform decisions about whether further testing of an intervention is warranted"*. Being aware of which features of the intervention and sample in the pilot study are not scalable or generalizable to the next stage of testing in a larger effectiveness trial - might optimize trial implementation[23]. Context and implementation are critical to the extent of an intervention's effect, especially in complex interventions[24]. Therefore, different approaches regarding effectiveness research have been suggested to improve our understanding of generalizability, stressing the need for process evaluations to understand an intervention's mechanisms of action[25]. Once identified, then larger trials, with integral process evaluations can be conducted[25]. Especially missing data (due to drop out, attrition or item or questionnaire non-response) can introduce problems of selection bias, particularly if they are influenced by what arm study participants are allocated to, affecting generalizability[26]. As recruitment and retention rates of a large-scale trial can differ from the pilot study, an additional strategy in the development phase of an intervention is pre-emptively generating strategies to address potential recruitment and retention difficulties via focus groups and interviews with the target group[27].

In general, there is little evidence that helps researchers to make well-informed decisions about how to do their trials[28]. Performing a Study Within A Trial (SWAT) - which is a self-contained research study that has been embedded within a host trial with the aim of evaluating

or exploring alternative ways of delivering or organizing a particular trial process - might contribute to more evidence-based decisions within trials. However, especially in trials testing psychosocial interventions for children with cancer and their parents this might be challenging because undertaking SWATs includes challenges such as increased complexity and management burden, which are more profound in pediatric populations due to a perceived increased patient vulnerability or risk[29].

A strength of this study is the high participation rate from the researchers (75%) we approached, showing that recruitment and retention are experienced as challenging and recognized as important. Moreover, our search strategy to select cases limited the risk of missing relevant trials. Including the PI as well as other research staff in the interviews allowed us to gain an in-depth understanding of the recruitment and retention challenges and strategies.

A limitation of this study is that the overall number of included studies was low, so drawing conclusions must be done with caution. Additionally, we included studies that were registered from 2011 onwards, leading to an increased risk of recall bias for some studies. However, we noticed that, in most interviews, the respondents complemented each other when not remembering something, and some respondents could compare experiences from the selected case to follow-up trial studies of the intervention they were undertaking now, enriching the information. Another limitation is that we based our selection of cases on a search string in English, possibly missing relevant studies reported on in other languages. A final limitation is that the analysis was done by one researcher, although main findings were discussed with the core research team to enhance reliability of interpretations.

CONCLUSION

We identified a paucity of evidence on experienced recruitment and retention challenges and best practices on optimizing them. Respondents indicated that even after years of experience of conducting studies in this field, it is difficult to know in advance what strategies will have desired effects. Effectiveness of 'new' strategies is challenging to map because they are often used in combination with other strategies and in pediatric studies, the number of eligible participants is generally low and effectiveness cannot be directly attributed to the use of only that particular strategy or to other factors such as more eligible participants in that particular period for example. Additionally, what may have worked in a former variant of the study might not necessarily work in a different variant of the study due to contextual factors. However, some studies had high enrollment and retention rates and managed to overcome challenges successfully, which indicates that suitable recruitment and retention is possible. The close follow-up of families and maintaining regular contact with the key persons at the recruitment sites while continuing a flexible attitude to the extent possible was emphasized most often. The strategies outlined in this study can help researchers to optimize their protocol and implementation of the trial and contribute to better psychosocial care for children with cancer and their parents.

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522

Statements and Declarations

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Ethics approval:

The project this study is part of was approved by the Medical Ethics Committee of the University Hospital of Brussels in Flanders, Belgium (B1432020000177). The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments and in compliance with our institutional guidelines.

Consent to participate:

Informed consent was obtained from all individual participants included in the study.

Consent to publish:

All respondents provided informed consent for publication of the study characteristics and use of quotes.

Author Contributions:

All authors contributed to the study conception and design. Anne van Driessche performed the interviews and analysis, drafted the initial manuscript, and adapted the manuscript. Prof Kim Beernaert, Prof Joachim Cohen, Prof Luc Deliens, Dr Marijke C. Kars and Prof Aline De Vleminck critically reviewed and revised the manuscript. Dr Maureen E. Lyon, Dr Maru Barrera, Dr Veronica Dussel, Dr Pernille Bidstrup, Dr Abby R. Rosenberg and Dr Terrah F. Akard participated in the study as a respondent sharing expertise on the topic of interest, and critically reviewed and revised the manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Tables

Table 1. Search string for Pubmed (January 2022)

"Randomized Controlled Trials as Topic"[Mesh] OR "Random Allocation"[Mesh] OR "Program Evaluation"[Mesh] OR trial*[tiab] OR test[tiab] OR effect*[tiab] OR "control group"[tiab] OR "intervention group"[tiab] OR random*[tiab] OR "test effectiveness"[tiab]
And
"Psychosocial Intervention"[Mesh] OR intervention*[tiab] OR program*[tiab] OR "psychosocial intervention"[tiab] OR "psychological intervention"[tiab] "Patient Education as Topic"[Mesh] OR "Psychotherapy" [Mesh] OR "Quality of Life" [Mesh] OR "Resilience, Psychological"[Mesh] OR "Adaptation, Psychological"[Mesh] OR "communication"[tiab] OR "Communication"[Mesh] NOT "Therapeutics"[Mesh] NOT "Medication Therapy Management"[Mesh] NOT medication*[tiab] NOT "Pharmacology"[Mesh]
And
"Child"[Mesh] OR "Adolescent"[Mesh] OR child*[tiab] OR adolescent*[tiab] OR "adolescent patient"[tiab] NOT "Cancer Survivors" [Mesh] NOT "cancer survivors"[tiab]
And
"Neoplasms"[Mesh] OR neoplasms[tiab] OR "Pediatrics"[Mesh] OR "pediatric cancer"[tiab] OR cancer[tiab] OR "pediatric oncology"[tiab]
Filters used: - Time period from 2011/1/1/ - 2022/1/1 - Study type: Randomized Controlled Trial - Age: Child (Birth – 18 years)

Table 2. Inclusion- and exclusion criteria for the selection of studies

Inclusion criteria	Exclusion criteria
1. Target group of the intervention is children / adolescents with cancer up until 25 years old (with at least n=5 children recruited younger than 18 years old)	1. Pharmacological studies
2. Parents are included in the study (not necessarily involved actively in the intervention itself, but involved in, for example, filling out questionnaires)	2. Studies involving medical devices
3. The intervention has psychosocial components and is being tested in an individually randomized controlled trial	3. Cluster RCTs or RCTs in which the control group receives an active comparator (such as attention control)
4. The child / adolescent and parent(s) are randomized in an intervention group and control group with care as usual	4. Studies registered before 1 January 2011
5. Studies are registered after 1 January 2011	

Table 3. Key characteristics of selected studies for which we held interviews

Selected studies	Function of the participants in the interview	Target population Country, sites and timing Timepoints of surveys	Intervention goal and content	Original target goal and time window of recruitment as defined in protocol/trial register	Actual number of participants enrolled and time window of recruitment. Extra time/sites required?	Enrollment rate[1] and retention rate[2] and extra time or sites required
1. Promoting Resilience in Stress Management (PRISM)[30]	One Principal Investigator and two research assistants.	**Target population:** Adolescents and young adults (13 – 25 years old) diagnosed with cancer between 1- and 10-weeks prior to enrollment OR ever diagnosed with progressive, recurrent or refractory cancers and receiving systemic chemotherapy and their parents **Country, sites and timing:** USA	**Goal:** To bolster resilience skills, and, in turn, to improve participant-reported quality of life, hope, and mental health outcomes. **Intervention components and delivery:** - Stress management skills (breathing, relaxation, mindfulness) - Goal-setting skills (creating and pursuing	**Original target goal:** 100 **Original time window of recruitment:** 24 months	**Actual number of participants enrolled:** 99 **Actual time window of recruitment:** 22 months **Extra time or sites required?:** no	**Enrollment rate:** 77% **Retention rate:** 92% among subjects well enough to participate; 75% among all subjects, including those who died during the study.

[1] Enrollment rate: defined as the proportion of people who enrolled out of all people determined to be eligible
[2] Retention rate: defined as the proportion of people who enroll and who complete the study

		- Seattle Children's Hospital (January 2015 – October 2016) **Timepoints of surveys:** Baseline, and abbreviated surveys measuring only the primary endpoint at 2- and 4- months post-enrollment. A final and comprehensive survey 6-months post-enrollment.	"SMART" [Specific, Measurable, Actionable, Realistic, Time-dependent] goals - Cognitive-restructuring / positive reframing (identifying negative self-talk, reframing experiences and perspectives to make them feel manageable) - Benefit-finding / meaning-making (identifying gratitude, purpose, meaning, identity) Delivered by trained, non-clinical college graduates in 4 scripted 30 – 50 minute, 1-on-1 sessions approximately every other week.			
2. Enhanced Psychosocial	One Principal Investigator and	**Target population:**	**Goals**: Improve children's and	**Original target goal:** 40 dyads -	**Actual number of participants**	**Enrollment rate:** 54%

Intervention (EPSI)[31]	one project manager.	Dyads of youth (10 – 17 years old) newly diagnosed with cancer (within 4 weeks of diagnosis) and their primary caregiver and siblings **Country, sites and timing:** Canada -SickKids Hospital (Toronto) (Nov 2017 – April 2019) **Timepoints of surveys:** Near diagnosis (T1) and 12 months later (T2)	family coping with disease-related stressors such as pain and uncertainty, improve child mood and enhance social engagement with peers. Improve the triaging of resources and enhance the effectiveness of psychosocial intervention for children with cancer. **Intervention components and delivery:** 1) Information about the psychosocial risk of the family and mental health of the child 2) Sharing screening results and	one caregiver, one target child **Original time window of recruitment:** 16 months	**enrolled:** 38 dyads **Actual time window of recruitment:** 17 months **Extra time or sites required?:** start of the study was delayed for 6 months due to COVID-19 pandemic	**Retention rate:** 90%

			recommendations with the treating team and with the family 3) The Psychosocial Navigator as resource for tailoring psychosocial resources to child-family distress, linking with the clinical treating team			
3. PediQuest (PQ)[32] followed by the PediQuest Response Study[33,34]	One Co-Investigator and one project manager.	**Target population:** Children >2 years old with at least a 2-week history of progressive, recurrent, or non-responsive cancer or for whom there was a decision not to pursue cancer-directed therapy, and their parents **Country, sites and timing:** USA - Dana Farber	**Goal:** to improve quality of life in children, adolescents, and young adults with advanced cancer, and their parents **Intervention components and delivery:** PediQuest Response includes an enhanced system (web-based and with an app for answering	**Original target goal:** 200 child-parent dyads (to end up with at least 136 randomized) **Original time window of recruitment:** 3 years	**Actual number of participants enrolled:** 196 (155 randomized) **Actual time window of recruitment:** 3.5 years **Extra time or sites required?:** yes	**Enrollment rate:** 66% **Retention rate:** 81%

		Children's Cancer and Blood Disorders Center, Children's Hospital of Philadelphia, Seattle Children's Hospital, Texas Children's Hospital (April 2018 – July 2022) **Timepoints of surveys:** Weekly surveys for 16 weeks in total after randomization (after a run-in period of 2 weeks)	surveys and viewing reports) that is coupled with early integration of a palliative care consulting team.			
4. FAmily-CEntered pediatric advance care planning for teens with cancer (FACE-TC)[35]	One Principal Investigator, one Site Principal Investigator and one research coordinator.	**Target population:** Adolescents with cancer 14 – 21 years old and parents **Country, sites and timing:** USA - Akron Children's Hospital,	**Goal:** to facilitate goals-of-care conversations and completion of advance directives between AYAs and their families. **Intervention components and delivery:**	**Original target goal:** 130 adolescent/family dyads (total of 260 participants) **Original time window of recruitment:** 2 years, 3 months	**Actual number of participants enrolled:** 130 adolescent/family dyads **Actual time window of recruitment**: 2 years, 9 ½ months	**Enrollment rate:** 39% (benchmark was 50%) **Retention rate:** 84% (104 of 126 dyads) retention at the 18-month assessment

		Children's National Hospital, St. Jude Children's Research Hospital, University of Minnesota Masonic Children's Hospital (July 2016 - April 2019) **Timepoints of surveys:** Baseline and at 3-months postintervention.	Three 60-minute sessions with a certified facilitator at weekly intervals. Session 1: the Lyon Advance Care Planning Survey administered separately to AYAs and families to prepare the dyad for session 2 conversations Session 2: the Respecting Choices Next Steps pACP-facilitated conversation Session 3: the completion of the Five Wishes advance directive A protected email with a summary of the conversations and including a copy of the statement of		**Extra time or sites required?:** 1 year no-cost extension and additional time to complete final analysis and publications. 2 extra sites added.	

			treatment preferences and Five Wishes were sent to the treating oncologist.			
5. Legacy intervention[36]	The Principal Investigator.	**Target population:** Children 7-17 years old with advanced cancer and their parents (advanced cancer defined as relapsed or refractory cancer determined by parent self-report) **Country, sites and timing:** USA - Advertisements were placed on Facebook over a 3-year period (2015 – 2018) **Timepoints of surveys:** Baseline (T1), post-intervention (T2) and an intervention	**Goal**: reduce suffering of children with cancer and caregivers by improving parent-child communication and coping strategies and adjustment outcomes **Intervention components and delivery:** A website guided children to create a personal digital storyboard by directing them to: a) answer legacy-making questions; b) upload photographs; c) upload video, and d) upload music,	**Original target goal:**170 child-parent dyads **Original time window of recruitment::** 3 years	**Actual number of participants enrolled:** 150 child-parent dyads **Actual time window of recruitment:** 3 years **Extra time or sites required?:** No	**Enrollment rate:** 55% **Retention rate:** 72%

		process survey at study end (T3). The median time between T1 and T2 was 69 days (range 7 – 176) for children and 68 days (range 7 – 176) for parents.	and children were asked to complete it within 2 weeks. The website generated a unique electronic link that the coordinator emailed to the child or parent.			
6. Family-Oriented Support intervention (FAMOS)[37]	The Principal Investigator and the project coordinator.	**Target population:** Families of children in the age range of 0 – 6 years diagnosed with any kind of cancer. Curative intensive treatment had to be completed within 4 months. Children with leukemia could enter when receiving maintenance chemotherapy. **Country, sites and timing:** Denmark -	**Goal:** Targeting psychological symptoms in the whole family after the end of childhood cancer treatment **Intervention components and delivery:** Delivered face-to-face at home by 1 of 3 psychologists with experience in cognitive behavioral therapy. 3 – 7 face-to-face 1 – 1.5 hour sessions at home	**Original target goal:** 300 families **Original time window of recruitment:** 3 years	**Actual number of participants enrolled:** 109 families, 204 parents **Actual time window of recruitment:** 3 years and 7 months **Extra time or sites required?:** 7 months recruitment extension at all 4 sites	**Enrollment rate:** 63% **Retention rate:** No families dropped out. 79% provided 6-month and 53% provided 12-month assessment.

		University Hospital Rigshospitalet, Aarhus University Hospital, Odense University Hospital and Aalborg University Hospital. (August 2014 – March 2018) **Timepoints of surveys:** Baseline, 6 months after randomization and 12 months after randomization.	within 6 months of inclusion. Session 1 – How cancer has affected us as parents and as a family Session 2 – How we coped with cancer Session 3 – The family's future Session 4 – Children's session: the family before, during and after cancer Session 5 – Children's session: how to move on Booster – What have we learnt?			
7. Benefits of Obtaining Ownership Systematically Together in pediatric Advance	[3]Two data collectors.	**Target population:** Children aged 10 – 18 years with any kind of cancer in any stage,	**Goal**: to improve parent-adolescent communication on Advance Care Planning (ACP) themes	**Original target goal:** 86 **Original time window of**	**Actual number of participants enrolled:** 49 **Actual time window of**	**Enrollment rate:** not available yet **Retention rate:** not available yet

[3] The executive researcher of this project (AvD) was the interviewer.

Care Planning (BOOST pACP)[38,39]		together with at least 1 parent **Country, sites and timing:** Belgium - University Hospitals of Antwerp, Leuven, Brussels and Ghent (March 2021 – March 2023) **Timepoints of surveys:** At baseline (T0), at 3 months from baseline (T1) and at 7 months from baseline (T2).	**Intervention components and delivery:** The core components include: 4 ACP conversation sessions with the adolescent and/or parent(s) provided by a trained facilitator, structured by interactive conversations cards covering different ACP themes, followed by a transfer of information from the intervention facilitator to the pediatric oncologist.	**recruitment:** 2 years	**recruitment:** 2 years **Extra time or sites required?:** no, one site dropped out, because their pediatric oncology ward closed down during the recruitment period	

Table 4. Main strategies for addressing recruitment and retention challenges

Eligibility
Broaden the inclusion criteria to the extent possible allowed by the intervention's goal and content. Determine eligibility criteria before the start of the study and make reliable estimates of the number of families adhering to these criteria. When determining the eligibility criteria, collaboration with healthcare professionals or national cancer registers is recommended.
Use **a thorough screening process** to make sure eligible families are not missed in the various steps of the study. This requires a monitoring system, informed by access to medical records and patient lists or by regular meetings with healthcare professionals.
Closely involve the recruitment sites before the start of the study to discuss appropriate ways of introducing the study to potential participants. - *Discuss inclusion criteria and implications* with healthcare professionals. - Take the time to *"learn who your allies are"* at the hospital. Who is intrinsically motivated to commit her/himself to the study tasks? - *Explore whether study tasks could be a formal part of the healthcare professional's tasks*. Not as an additional task, but replacing an existing task. - *Arrange a reimbursement for collaborating healthcare professionals* (e.g. an hourly rate or per number of approaches). - *Arrange research assistant/data collector access to medical records* (or to the hospital system, if possible) *or arrange a monthly timepoint* to obtain a list of eligible people. - *Discuss patient eligibility regularly, or discuss beforehand the option of following an opt-out procedure:* inform the primary oncologist (via email) that you will contact the eligible family about the study. Only if the oncologist disagrees, will he/she will respond (via email) asking you not to contact the family within a certain time period. - *Create buy-in* by planning implementation and sustainability activities, such as: presentations at the ward, regular visits with small presents, or disseminating newsletters on the project. - *Provide the different recruitment sites with materials that facilitate introducing the study*. Develop flyers and ask permission to leave them in places visited often by parents and children, such as waiting rooms, kitchens, and the reception desk.
If possible, **apply for a special grant that provides support for the initial development of clinical trials** (such as the NIH Planning Grant Program (R34)) in the USA. This money can be used for time spent on arranging contracts with the various sites you are recruiting from.
Enrollment
Provide continuous training for the research staff. When hiring (new) research staff, remember that they need to be: 1) flexible in their availability and way of working; 2) relatable to study participants or having experience in working with them; 3) motivated and passionate about the theme. **Be transparent with your (potential) staff** regarding the kind of study population and how they might engage with you, and the flexibility you expect. This helps prevent staff turnover.
Involve the recruitment sites and the patients/families before the start of the study to determine appropriate ways of introducing the study to potential participants.
Communicate the experiences of families who have participated to the healthcare professionals and eligible participants (e.g. via newsletters, flyers or during presentations at the wards).
Have research staff follow up closely and be present at the sites regularly.

Offer a relevant intervention for you target group and design the intervention in a flexible way by involving your target group beforehand.
Increase your study's visibility by using attractive materials (for example) and think about efficient ways to distribute them (such as patient organizations, hospital wards, local health insurance fund magazines), so that people might see information about the study beforehand.
Optimize the study's introduction by research staff: - *Put measures in place* to avoid situations (such as bad news, heavy treatment) that can make the timing of the study introduction inappropriate. Use a personalized and stepped approach (sometimes only plant the seed and follow up quickly). - *Be as flexible as possible in introducing the study*. Some families do not like to be approached in the clinic because they are eager to get out of there - they prefer to be contacted at home. - *Make sure the families have heard about the study* from healthcare professionals or via a flyer or email before your first call. - *Explain what the goal of the intervention is,* why this is important and how this may contribute to a better quality of life and why the effectiveness of the intervention is being studied. - Have *a basic understanding of the diagnosis* as context in approaching the family. - *Use a short pitch* not exceeding 2 minutes. - *Use lay language.* - *Talk to the parent and child together and engage with the child*. Experience shows that, when you talk to them together, parents will participate if their child wants to participate. Respondents have often experienced that the child has the final say. - *Make their participation feel important*. Mentioning that their participation can help other families in a similar situation can help. - *Acknowledge the participants' difficult situation*, be sensitive and consider the family burden. - *Emphasize the minimal burden in participating,* and explain how participation has been made as easy as possible. - *Respond to reasons* for them not wanting to enroll.
Retention
Be flexible when offering moments to visit the participants, and be on top of non-response by closely monitoring - and then contact the participants as soon as possible when they have missed their measurement.
Provide consistency in contact between the research staff member and the families
Facilitate filling out surveys as much as you can. Provide electronic as well as paper versions and shorten them if possible. Prioritize having the items on your primary outcome filled out. Have a language consultant look at the items of your questionnaire to optimize understandability, especially when you have developed the items yourself.
In the USA studies, in particular, **monetary incentives** were given to the participants and, in some cases, the incentive was mentioned on the recruitment materials. However, not every respondent was convinced about the effectiveness of this. A small increase in the monetary incentive per timepoint might work best.
Provide for flexibility in the intervention process by offering a range of time to enable alignment with the participants' situation.
If your study is longitudinal and entails surveys being filled out at different timepoints, **building in a run-in period** can help preventing enrolling participants who will most likely drop-out. A run-in period means that, prior to randomizing a family, a family fills out several surveys to see whether they will be engaged in the study or not. Providing this

opportunity was seen as less intimidating for families than, for example, committing to an 18-week intensive study for example.
General strategies
Perform a pilot study in the target group in advance, preferably in a situation similar to that of the larger scale study (e.g. involve more recruitment sites already). This will give insight into expected enrollment rates, as well as contribute to establishing better monitoring systems to assess eligibility, ways of cooperating with healthcare professionals, and give the opportunity to slightly adapt the intervention if you find that some components are not working in practice as expected.
Include a plan in your protocol for changing recruitment strategies, concretizing different scenarios: e.g. if the enrollment rate is less than x%, we will use strategy number 2). Having IRB approval upfront to use these strategies, will save time.
Explore other recruitment 'sources' such as social media, making a video, using email lists from the university or hospital, involving patient organizations. Pilot test these other sources, if possible. When recruiting via Facebook ,for example, an algorithm needs to be developed, monitored and adapted continuously, and so involving specialists might be worthwhile. Critically appraise whether your target group is appropriate: if the target group is quite narrow in terms of diagnosis and time since diagnosis, social media might not be suitable.

Table 5. Challenges in recruitment and retention and strategies to overcome them per major theme

Challenges and illustrating quotes (study from Table 3)	Strategies and illustrating quotes (study from Table 3)
Eligibility	
1. Balancing number oriented pragmatism with intervention specificity *"Especially in psychosocial studies narrow inclusion criteria can add rigor. We knew that a 12 year old and a 22 year old were vastly different in the ways they were experiencing their cancer and their development. Scientifically, you could argue that it is better to focus on a narrower group of patients because you are meeting that particular age group's needs, but at the same time you can't enroll that many people if your criteria are too narrow."* (1. Promoting Resilience in Stress Management (PRISM))	**1. Broaden the inclusion criteria to the extent possible allowed by your intervention's goal and content.** *"We expanded that: you no longer had to have a history of a recent recurrence and we started to say well the whole experience of a recurrent cancer can be pretty stressful because of these constant spikes of uncertainty."* (1. Promoting Resilience in Stress Management (PRISM))
2. Gatekeeping from healthcare professionals *"In 8% of the cases, the principal investigators who were healthcare professionals themselves had validated their eligibility, but the primary oncologist had told us "no". This was very variable by site, but most often individual clinicians that were problematic."* (3. PediQuest Response)	**1. Closely involve the recruitment sites before the start of the study to discuss appropriate ways of introducing the study to potential participants** *"It's necessary to involve people from the recruitment sites, that they are aware what the study entails, and what the tasks for them entail. That they won't be surprised because their actual tasks turned to be much more time-intensive than discussed. Concretely discuss with them who is responsible for what.. and during the recruitment period of 2 years, a lot can happen so it's important to regularly ask them if they are still up to doing those tasks."* (7. Benefits of Obtaining Ownership Systematically Together in pediatric Advance Care Planning) (BOOST pACP))
"For some other trials currently, at some of the sites they have systems where the patient primary oncology provider required them to get it approved and we have run into issues where oncologists will arbitrarily say no, and of course it's not	**2. Use a thorough screening process to make sure eligible families are not missed in the various steps of the study. This requires a monitoring system, informed by access to medical records and patient lists or by regular meetings with healthcare professionals.**

completely arbitrarily, but we have had a scenario in some sites where there were 50% of eligible patients and the oncologists were just like 'I think they are too distressed' or 'this kid is going to college soon'. You have to kind of figure out ways to like.. respectfully listen to those things, and try to give every family the opportunity to say no to us rather than someone else opt them out." (1. Promoting Resilience in Stress Management (PRISM))	*"...following up with the research assistants at each site twice a week, having frequent meetings, using these reports and doing these intensive processes, we were still only able to approach 60% of people that we found to be eligible. So another 40% that became ineligible.. we were waiting to approach for various reasons and changes in their disease criteria or transferred care or died or other things. So we kind of lost big chunks as part of the process. That made it really important that we started with everybody."* (3. PediQuest Response)
3. Having to involve multiple sites to increase the pool of eligible participants *"In the beginning it was difficult to find people at the wards that wanted to be our main contact points during the 2 year study period. And throughout the study, we noticed the different sites sometimes slightly adjusted the way of approaching patients to make it more feasible for them. At the beginning, we wanted to keep control but that is challenging. It takes time and effort to find ways that work for everyone"* (7. Benefits of Obtaining Ownership Systematically Together in pediatric Advance Care Planning) (BOOST pACP))	**1. Create buy-in by planning implementation and sustainability activities at recruitment sites.** *"...it depended on study site... at one site we were very reliant on oncologists going through their lists, we had one key person who had a good buy-in for this study. She made sure we had the names of people who fitted our eligibility criteria."* (4. Family-Centered pediatric advance care planning for teens with cancer (FACE-TC)) **2. Arrange a reimbursement for collaborating healthcare professionals (f.e. an hourly rate or per number of approaches)** *"we kept a log of every time the contact nurses approached a patient, not necessarily if they were successful, as recruiting them, but just to approach a patient. I think for every 5, we gave them a 5 dollar Starbucks giftcard. And it was a pretty good incentive, people really liked the coffee*." (2. Enhanced Psychosocial Intervention (EPSI))
"We have spent the first year of the trial just to get contracts and agreements that we can share protected health information with other sites and some of them took up over a year." (4. Family-Centered pediatric advance care planning for teens with cancer (FACE-TC))	**3. If possible, apply for a special grant that provides support for the initial development of clinical trials** *"They have a mechanism now, called an R34, you can now have 2-3 years to just set the trial up, so we have spent the first year of the trial just to get contracts and agreements that we can share protected health information*

	with other sites and some of them took up over a year and some of them and I ended up travelling to some sites to review and that burned up money too." (4. Family-Centered pediatric advance care planning for teens with cancer (FACE-TC))
Enrollment	
1. Perceived difficulty introducing the study to families in this burdensome situation and staff turnover during a long recruitment period *"During the windows of staff turnover our enrollment would go down because people were either less available or less skilled at having the conversations and building rapport with the families."* (1. Promoting Resilience in Stress Management (PRISM))	**1. Provide continuous training for the research staff.** *"Mock exercises are really helpful. We did activities like having someone to write down what their pitch would be and then another research assistant look at what she has and finding templates and cut out content. Simplify, simplify, simplify!"* (3. PediQuest Response) *"We hold weekly research meetings, in which we do sometimes role plays. Those meetings were not just to find out in terms of numbers but also what is working, how could we improve, what other strategies could we use. These are critical in building the skills of the research staff, but also providing peer support and positive energy to keep that persistence."* (2. Enhanced Psychosocial Intervention (EPSI)) **2. Be transparent with your (potential) staff** regarding the kind of population, how the population might engage with you and what kind of flexibility you expect. This contributes to preventing staff turnover. *"transparency with your staff is key, from the beginning be like this is the population, this is how they like to engage with you, here is what we expect in flexibility. The flexibility piece was major in helping us with recruitment and retention. As we mentioned earlier, there are weekends and evenings, and home visits where people felt safe. Because you might have staff members that say I cannot meet those expectations, but it might help if you tell them early on, their brain gets programmed in a way, that this is how I'm going to engage in it and interact with the participants*

	from the study." (4. Family-Centered pediatric advance care planning for teens with cancer (FACE-TC))
2. Making realistic estimations of willingness to participate *"We didn't really appreciate how stressful the actual study might be to people, even if we know what might be helpful… It's really a factor of us overestimating people's willingness to participate"* (1. Promoting Resilience in Stress Management (PRISM)) *"Our study was on symptoms and some people don't want to think about the symptoms. Because if you felt nauseous, would you sit and talk about how you are nauseous? Sometimes people felt like acknowledging the symptoms and thinking about them made them feel worse."* (3. PediQuest Response)	**1. Involve recruitment sites and patients/families to determine appropriate ways of introducing the study to potential participants.** *"Involving people in how should we set this up, how do you want this, and developing a sort of community between those who recruit and that they have a shared task to solve together."* (6. Family-Oriented Support Intervention (FAMOS)) *"Ideally, we should have engagement from young people and their parents doing the design of the study. And thinking about relevant strategies for recruitment. They can tell us more on what they like or what they don't like and what will be useful."* (2. Enhanced Psychosocial Intervention (EPSI)) **2. Communicate the experiences of families who participated to the healthcare professionals and eligible participants (f.e. in newsletters, flyers or during presentations at the wards).** *"And also, for them to hear about how it was for the families. and why are we doing this of course. It's very important to communicate that. And I think that's for our future studies also very important that they sort of know it's not only about recruitment, it's also about the family is getting better. And what do the families gain from this. I think that could be done even more, for them to be aware of that all the time. Perhaps hearing some of the families and hearing about what they have experienced in the project."* (6. Family-Oriented Support Intervention (FAMOS))
3. Competing studies *"Oncology patients are in trials for almost everything that they do. They consented before about biobanking of their tissue and sperm,*	-

for their enrollment in other clinical trials. I think some of the exhaustion comes from that they do not want to hear about anóther clinical trial." (4. Family-Centered pediatric advance care planning for teens with cancer (FACE-TC))	
4. The randomization aspect *"I do see occasions that people say no, because they say "I'll do it if you can promise me I don't have to do the program" or "if you can promise me that I do the program"."* (1. Promoting Resilience in Stress Management (PRISM))	**1. Use lay language** *"Randomization is a very difficult concept for people to grasp. So developing easy language, easily understood for people what does randomization actually mean."* (4. Family-Centered pediatric advance care planning for teens with cancer (FACE-TC))
5. The dyadic nature of enrollment *"Being able to reach families really is the most difficult challenge in this trial. Because it's a study involving a child, you need the signature for consent from both parents. It takes a lot of calls and reminders to get this last signature. They often still have to discuss participation within the family, and they sometimes forget, so it takes a lot of time."* (7. Benefits of Obtaining Ownership Systematically Together in pediatric Advance Care Planning) (BOOST pACP)) *"but then also to recruit kids, you have to recruit their parents, and sometimes that's very challenging, because sometimes you have a kid, who you think might be super excited but you have a parent that doesn't want them to do it for some reason, so it's hard to get everybody on board. It's also hard: the nature of children with advanced cancer. The illness is such a rollercoaster, it's like how the stars are aligned, if they are feeling good and schedules align or whatever to have them complete the intervention session.* (5. Legacy Intervention)	**1. Close follow-up by research staff and being present at the sites regularly.** *"Compared to a former FACE study, the recruitment was more difficult in this study. The staff this time had a lot of other things to do, although of course they were also very dedicated. But the first staff was only focused on the FACE study. They had more hands-on follow-up, or maybe they were on the ground a little bit more, in the clinic areas."* (4. Family-Centered pediatric advance care planning for teens with cancer (FACE-TC)) **2. Talk to the parent and child together and engage with the child.** *"if we were able to convince the child, then it was a go. So the parent would only do it of the child wanted to do it, never did you see the opposite. So that was interesting…. the other thing is that sometimes with parents, when they are overwhelmed, assume sometimes that their child does not want to participate. So I found it was really good to be talking to them together about the study. And sometimes they would just project their own.. to the child and the child was sometimes like, yeah I have got*

"Ideally, we wanted the nurses to talk to parents in the hospital, but some of the parents would be at home or just coming for a quick check-up. It was difficult to catch them physically." (6. Family-Oriented Support Intervention (FAMOS))	*nothing else to do, I'm here in bed anyway."* (2. Enhanced Psychosocial Intervention (EPSI)) **3. Offer a relevant intervention for your target group and design the intervention in a flexible way by involving your target group beforehand** *"And I think that's the most important part, is to offer something that is relevant to people. And I think the only way to do that is to involve the families and for you study maybe the adolescents? In both how do we sort of design and set-up that's most relevant to your family and also, maybe get them on board on how to do the recruitment. ...I think the fact that there was a combination of very concrete tools and then videos. And it was homebased, that was the main thing. And we were very flexible in terms of, we tried to do it on their terms. I think that were the most important things that made them feel that was comfortable for them as well."* (6. Family-Oriented Support Intervention (FAMOS))
6. Finding an appropriate time to introduce the study to the family *"It's SO dependent on the family and it's really hard to tell from a chart note or even like a conversation with the provider, because I think that different providers have different interpretations of when a family is ready or if they think they are receptive."* (1. Promoting Resilience in Stress Management (PRISM))	**1. Put measures in place to avoid situations that can make the timing of the study introduction inappropriate. Use a personalized and stepped approach.** *"We do have an eligibility criteria as part of our approach checklist that asks if a family had a sort of serious conversation in the last two weeks, or if the kid is going through scans that day and might get bad news then we wouldn't approach them that day, or if we could see through the record that last week they found out about a progression, they wouldn't be eligible until 2 weeks after that.. and then sometimes information would come out of meeting a family, so we might come back to them one month later.. we might go and talk to them and say you know, can we tell you about this study.. and they will tell us 'our grandpa had just died' and we are trying to figure out the funeral next week.. and we are so overwhelmed right now.. so you could say would it be okay if I would check in with you again in a month.. in some sites we leaned more on that than in others*

	again I would say, but that was something that we would certainly try to kind of personalize or approach each family and adopt as much as we could to make it as convenient as possible." (3. PediQuest Response) *"In a survey we asked teenagers when do you want to be approached and most of them said from the time of diagnosis, so it was really based on their feedback that it was okay to talk about this stuff from the time of diagnosis. And we quickly checked with the provider, is there a particular reason we shouldn't approach today….If they were having a spinal tab, that was not the day, so sometimes we would just plant the seed, but then we came back later."* (4. Family-Centered pediatric advance care planning for teens with cancer (FACE-TC))
7. Unanticipated circumstances (e.g. COVID-19 pandemic). *"also a key part here is the face to face contact. With COVID and so on made it much more challenging."* (4. Family-Centered pediatric advance care planning for teens with cancer (FACE-TC)) "*our visibility and presence in the hospitals would have been better if it wasn't for the COVID pandemic. We would have been more present at the hospital wards and personal contact always helps in making things happen. The COVID pandemic gave us a false start."* (7. Benefits of Obtaining Ownership Systematically Together in pediatric Advance Care Planning) (BOOST pACP))	**1. Increase your study's visibility by using attractive materials (for example) and think about efficient ways to distribute them (such as patient organizations, hospital wards, local health insurance fund magazines magazines), so that people might see information about the study beforehand.** *"Hanging flyers in the hospital ward and writing a testimonial from a family that participated in a local magazine of a patient organization and promoting this via the social media (such as LinkedIn or Facebook) of the participating hospitals helps increasing the visibility of your study. This won't necessarily lead to a higher number of participants, but families may recognize the study when they are formally introduced for the first time and this might contribute to them saying "yes" to participation a bit quicker."* (7. Benefits of Obtaining Ownership Systematically Together in pediatric Advance Care Planning) (BOOST pACP))
Retention	
1. Non-response and drop-out *"We may have had a slightly inflated rate of drop out from our intervention arm, so maybe for some people that was almost like*	**1. Be flexible when offering moments to visit the participants, and be on top of non-response by close monitoring.**

they hoped for the easiest study experience that took the least time and energy for them." (3. PediQuest Response) *"We followed our intervention group monthly. This was not the case for the control group, we got them a year later. We didn't retain as many in the control group because the people we were following on a monthly basis were engaged. In the control group, we may have lost as many as 25%."* (2. Enhanced Psychosocial Intervention (EPSI)) *"And I think that was part of the reason why we had attrition, especially in the control group. It was a lot of questionnaires for the parents to fill out, without sort of receiving any intervention."* (6. Family-Oriented Support Intervention (FAMOS))	*"The people that followed-up the families were very persistent. If the family said today is not a good day, they said: "can I call you tomorrow or can I check up on you in 2 weeks, and put that in my calendar?". In reports it is known that at some number of phone calls there is a diminishing return, they are not going to call you back after 4 or 5 phone calls, but up until that point, people were busy . So be very flexible and persistent, but not just one voicemail and then they are lost to follow-up."* (4. Family-Centered pediatric advance care planning for teens with cancer (FACE-TC)) *"On every Monday and Thursday, we receive from the system whoever did not answer a survey. As the project manager, I would contact the research assistant at that site and say please follow up with so and so. The next survey is on a Tuesday so let's call them when the next one is active, and that it might be a good time to pop by the clinic and give them the gift card. So it was a lot of monitoring to be on top of it when somebody missed a survey to reel them back in.*"(3. PediQuest Response) **2. Provide consistency in contact between the research staff member and families** *"I think the main piece of retention that was important was engaging the research assistants to form relationships with the families."* (3. PediQuest Response) *"I think that was a good strategy. That it was the same person that day that they had contact with along the way."* (6. Family-Oriented Support Intervention (FAMOS)) **3. Facilitate filling out surveys as much as you can.**

	"But I think of course, that shortening the questionnaires as much as possible is the best strategy. And at that time, we only had paper-based questionnaires and I think it helps today with the electronic ones as well." (6. Family-Oriented Support Intervention (FAMOS)) **4. If your study is longitudinal and entails surveys being filled out at different timepoints, building in a run-in period can help preventing enrolling participants who will most likely drop-out.** *"We have the run-in period built in that we have described as like a three survey prior to randomizing a family to kind of prove that they are going to be engaged in the study or not, and so we really invited people to test it out, which was a little less intimidating than committing to an 18-week, sometimes intensive study experience… it kinds of helps the quality of the data we are getting… one thing we have learned is that people who did not respond the first 2 surveys, were not going to respond after.. and instead, we decided to do this run-in period, and get rid of the non-responders, because they would not give you any valuable data."* (3. PediQuest Response) **5. In the USA studies, in particular, monetary incentives were given to the participants and, in some cases, the incentive was mentioned on the recruitment materials. However, not every respondent was convinced about the effectiveness of this. A small increase in the monetary incentive per timepoint might work best.** *"I think they do help decrease drop-out at certain timepoints, so that's how we used it. My strategy now is different than what we did in this study. If I would do it over, I would have had an increasing incentive, at each data assessment point that it would increase as the study goes, I would have had a small incentive for T1, just to get them going, I would not have had an incentive with completing the intervention, because of*

	that early attrition we would had in the beginning in the intervention group, we offered them an incentive when they completed the intervention." (5. Legacy Intervention)
2. Keeping per-protocol timelines versus required flexibility *"We had a window of enrollment for the study that was close to diagnosis and that made it a little tough. Because sometimes we lost kids because they went way off the window for enrollment. Sometimes, we bended the rules a little bit to keep it."* (2. Enhanced Psychosocial Intervention (EPSI)) *"I mean we reschedule sessions constantly, because the kid has a fever and is not feeling good, the mom's exhausted.. I mean there is so much to.. so you try to be flexible, but when you're too flexible.. the range between T1 and intervention sessions sometimes is massively different from what the protocol says, because we've tried to be flexible, but for a study it kind of messes stuff up."* (5. Legacy Intervention)	**1. Provide for flexibility in the intervention process by offering a range of time to enable alignment with the participants' situation.** *"I know that all the psychosocial research needs to be very structured and regimented, and I think that there is also something to be said about the nature, any nature of psychosocial research, and how we need to be flexible. Flexible within the inflexibility of research too. So I think that with a lot of our interventions, when I was still working on a study, you had to be as flexible as possible, you might have to push your session out 2 weeks, because a patient is very sick in the ICU, and doing that two weeks later, is just something you have to do, to best support the patient and family, because there is patient-centered care, and not just the research too."* (1. Promoting Resilience in Stress Management (PRISM)) *"one of our research coordinators met with a family on a Saturday in the local library. Because that was convenient for them. So we were very flexible: weekends, evenings, all of those things."* (4. Family-Centered pediatric advance care planning for teens with cancer (FACE-TC))
General challenges	**General strategies**
1. The numbers in the larger scale trial could turn out vastly different from the pilot study. *"We enrolled 80% if I'm remembering correctly of people who we approached in our pilot study. So we felt confident, people like this are going to participate. I believe that we anticipated a 70% enrollment for this randomized trial… but in our current bigger studies that are multi-site trials, we have not been close to 70%,*	**1. Perform a pilot study in the target group in advance, preferably in a situation similar to that of the larger scale study (f.e. involve more recruitment sites already).** *"Between PediQuest original and PediQuest Response, we did a pilot study regarding the next step of the intervention. And in that pilot study we also learned a lot about how to enroll and develop these kind of tracking systems."* (3. PediQuest Response)

we're at a 60% of enrollment at our institution, but other sites are closer to 50%, and there are a couple of things there I think about a lot.. number 1 in adolescent and young adult oncology the average enrollment rates are like 30 or 40%. They are generally far less than 50%. So I think our 70% was an overly optimistic and very lucky number to pick for us on that project. I think 50 or 60% is probably more reasonable, if not ambitious. And 30 to 40% is probably more realistic." (1. Promoting Resilience in Stress Management (PRISM))	*"I think just testing the different aspects of the study beforehand is the best way to get the most knowledge."* (6. Family-Oriented Support Intervention (FAMOS))
2. Having to pause enrollment because another recruitment strategy was not included in the initial protocol and there was no IRB approval for that strategy. *"one of the sort of set-backs was that this happened during COVID, so uniquely in our study we had a big transition in the middle, pausing enrollment and changing all of the IRB procedures to allow for virtual opportunities."* (3. PediQuest Response)	**1. Include a plan in your protocol for changing recruitment strategies, concretizing different scenarios.** *"We're trying to do that in studies now, as much as I can and study start up, I try to anticipate challenges, and I'll try and go ahead, and have like numerous recruitment strategies written in the protocol is options to have IRB approval on for those upfront, so f.e. in hindsight in this study, I wish I would have started the protocol with three recruitment strategies: social media, recruiting from the clinic, and Research Match. And I'm gonna start with number 1 but if that doesn't go well I'm going to add number 2, and number 3 and have all of them available. So write it up in front just to have the options."* (5. Legacy Intervention)
3. Finding a sufficient number of recruitment sites that are able to or want to participate. *"To get a sample for an RCT, looking it at how many sites you would need. (laughs) That was going to be a huge, massive study. Would be 8 -10 sites and this would be very expensive. An additional challenge we were faced with, was other competing studies. Vanderbilt is a research intensive university, you know, everybody is trying to recruit from the hospitals and clinics."* (5. Legacy Intervention)	**1. Explore other recruitment 'sources' such as social media, making a video, using email lists from the university or hospital, involving patient organizations.** *"Vanderbilt has an email distribution list, so you can create kind of like a brief study description and basically sends out an email blast, but this email distribution goes to like thousands of people, so it's Vanderbilt staff, faculty unit, and if people were eligible they could contact. And we used ResearchMatch, which is a Vanderbilt based.. it's like a database where families can sign up to be research volunteers, so you can kind of search*

"We shopped around a little bit for the five sites in the current study. They are not the initial ones we planned on, and one of the reasons for that are that some of the sites initiated some sort of automatic to palliative care teams for patients that met their criteria and made the patients ineligible." (3. PediQuest Response)	*for certain criteria and they'll see your description and you can kind of contact them in that way."* (5. Legacy Intervention)

Figure Legend

Figure 1. Flow chart of the selection process

**Studies meeting the inclusion criteria and invited for an interview: 1). PRISM*[30]*; 2) EPSI*[31]*; 3) PediQuest*[32]*; 4) FACE*[35]*; 5) Legacy*[40]*; 6) FAMOS*[37]*; 7) Cognitive Behavioural Therapy*[17]*; 8) Homebased Multimodal Symptom Management Program*[16]*; 9) BOOST pACP*[39].