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Preventing child mental health problems through parenting interventions in Southeastern Europe (RISE): Protocol for a multi-country cluster randomized factorial study

Lachman, Jamie; Heinrichs, Nina; Jansen, Elena; Bruhl, Antonia; Taut, Diana; Fang, Xiangming; Gardner, Frances; Hutchings, Judy; Ward, Catherine ; Williams, Margiad; Raleva, Marija; Baban, Adriana; Lesco, Galina; Foran, Heather

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Author names: Jamie M. Lachman,[1,2] Nina Heinrichs,[3] Elena Jansen,[4] Antonia Brühl,[3] Diana Taut,[5] Xiangming Fang,[6] Frances Gardner,[1] Judy Hutchings,[7] Catherine L. Ward,[8] Margiad Elen Williams,[7] Marija Raleva,[9] Adriana Băban,[5] Galina Lesco,[10] Heather M. Foran[4]

Author affiliations:

[1] Centre for Evidence-Based Intervention, Department of Social Policy and Intervention, University of Oxford, Oxford, UK

[2] MRC/CSO Social and Public Health Sciences Unit, University of Glasgow, Glasgow, UK

[3] Department of Psychology, Clinical Psychology, and Psychotherapy, University of Bremen, Bremen, Germany

[4] Institute for Psychology, Alpen-Adria-University Klagenfurt, Klagenfurt, Austria

[5] Department of Psychology, Babeș-Bolyai University, Cluj-Napoca, Romania

[6] School of Public Health, Georgia State University, Atlanta, Georgia, USA

[7] School of Psychology, Bangor University, Bangor, UK

[8] Department of Psychology, University of Cape Town, Cape Town, South Africa

[9] Institute for Marriage, Family and Systemic Practice – ALTERNATIVA, Skopje, North Macedonia

[10] Health for Youth Association, Chișinău, Republic of Moldova

Corresponding author: Jamie M. Lachman, jamie.lachman@spi.ox.ac.uk

Abstract

Background: Child mental health problems continue to be a major global concern, especially in low- and middle-income countries (LMICs). Parenting interventions have been shown to be effective for reducing child behavior problems in high-income countries, with emerging evidence supporting similar effects in LMICs. However, there remain substantial barriers to scaling up evidence-based interventions due to limited human and financial resources in such countries.

Methods: This protocol is for a multi-center cluster randomized factorial trial of an evidence-based parenting intervention, Parenting for Lifelong Health for Young Children, for families with children ages two to nine years with subclinical levels of behavior problems in three Southeastern European countries, Republic of Moldova, North Macedonia, and Romania (8 conditions, 48 clusters, 864 families, 108 per condition). The trial will test three intervention components: length (5 vs. 10 sessions), engagement (basic vs. enhanced package), and fidelity (on-demand vs. structured supervision). Primary outcomes are child aggressive behavior, dysfunctional parenting, and positive parenting. Analyses will examine the main effect and cost-effectiveness of each component, as well as potential interaction effects between components, in order to identify the most optimal combination of program components.

Discussion: This study is the first factorial experiment of a parenting program in LMICs. Findings will inform the subsequent testing of the optimized program in a multisite randomized controlled trial in 2021.

Trial registration: NCT03865485 registered in ClinicalTrials.gov on March 5, 2019.

Keywords: parenting; child behavior problems; factorial; optimization; cost-effectiveness

Introduction

Child mental health problems continue to be a major global concern, especially in low- and middle-income countries (LMICs) (Engle et al., 2011). The prevalence rate of mental health disorders among children and adolescents, such as internalizing and externalizing problems, is 10% to 20% (Kieling et al., 2011). Although there is limited up-to-date data on the prevalence of child mental health problems in the Republic of Moldova, North Macedonia, and Romania where the present study takes place, adolescent health data from the World Health Organization Health Behavior in School-aged Children (HBSC) 2013/14 survey showed that adolescents in the three countries reported poor health (Moldova: 21%, N. Macedonia 4%. Romania: 17%). Conversely, life satisfaction was perceived in a reversed manner by 91% of adolescents in Moldova, 80% in N. Macedonia, and 89% in Romania – which is the lowest in Europe (World Health Organization, 2016).

Children are particularly at risk of developing externalizing behavior problems in early childhood when faced with multiple risk factors, such as high rates of poverty, parental mental health problems, and child maltreatment (Deater-Deckard, Dodge, Bates, & Pettit, 1998). The early onset of child behavior problems also predicts later development of antisocial behavior, poor educational performance, juvenile delinquency, and crime (Reid & Patterson, 1989). This is particularly relevant in Eastern Europe countries where studies on adverse childhood experiences (ACE) have shown associations with subsequent mental health and behavioral problems in adolescence and adulthood (Hughes et al., 2019). The ACE study in Moldova found prevalence rates of 12% for physical abuse, 25% for corporal punishment, 12% for psychological abuse, and 3% for sexual abuse. In North Macedonia, 21% experienced physical abuse, 11% psychological abuse, 6% sexual abuse, 20% physical neglect, and 31% emotional neglect. In Romania, 27% reported physical abuse during their first 18 years of life, 24% reported psychological abuse, and 9% reported sexual abuse. Adverse childhood experiences

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in these countries were also associated with risks for poorer health in later life. Comparison to the students who hadn't experienced any adverse childhood experiences, students who had were significantly more depressive, abused substances more frequently, and were at greater risk of attempting suicide and engaging risky sexual behaviour (Baban et al., 2013; Raleva, Peshevska, Sethi, & World Health Organization, 2013; World Health Organization, 2018). Moreover, economic modelling studies show that the added public cost of early onset conduct disorder is 10 times that of children without such problems, with raised costs to multiple sectors including health care, justice and education systems (Scott, Knapp, Henderson, & Maughan, 2001).

Parenting programs have demonstrated effectiveness in reducing child behavior problems as well as harsh parenting and maltreatment (Chen & Chan, 2015; Furlong et al., 2013), with emerging evidence from rigorous trials in LMIC (Knerr, Gardner, & Cluver, 2013; Mejia, Calam, & Sanders, 2012). These programs typically aim to strengthen caregiver-child relationships through positive parenting and help parents to manage child behavior problems through effective, age-appropriate, nonviolent discipline strategies (Kaminski, Valle, Filene, & Boyle, 2008). Moreover, despite theory suggesting that very early interventions may be better, there is surprisingly little evidence for differential effects by age of parenting interventions on child behavior outcomes, with evidence suggesting that these interventions work well across the age range of two to nine years (Gardner et al., 2018). Recent meta-analyses also suggest that parenting programs are effective when transported from the country of origin to another country (Gardner, Montgomery, & Knerr, 2015), and that transported and homegrown programs may be equally effective as long as they are grounded in similar evidence-based principles and practices, and delivered by culturally competent implementers (Leijten, Melendez-Torres, Knerr, & Gardner, 2016).

Despite the emerging evidence of the effectiveness and transportability of parenting interventions in reducing child behavior problems and violence against children, many governments and service providers in LMICs face multiple challenges taking evidence-based parenting programs to scale (Mejia, Leijten, Lachman, & Parra-Cardona, 2016). Many parenting programs are too expensive to deliver effectively in low-resource settings due to their complexity and cost (Mikton, 2012). Programs also often fail to be implemented beyond the trial stage on a sustainable basis because they do not fit the local service delivery setting (Bumbarger & Perkins, 2008). As a result, it is essential that innovative research methodologies are employed in order to optimize parenting programs in LMICs so that they are 1) effective at reducing child behavior problems and harsh parenting, 2) efficient in terms of their utilization of available human, institutional, and financial resources, and 3) scalable in terms of their affordability, replicability, and sustainability.

Methods

Overview and study design

The RISE project (funded by the EU, Project Number 779318) aims to address this need by developing, optimizing, and testing an evidence-based parenting program, Parenting for Lifelong Health for Young Children (PLH Children), in order to reduce child behavior problems in families with children ages two to nine in three Southeastern European countries – one which is lower middle-income, Republic of Moldova, and two which are upper middle-income, North Macedonia and Romania (Frantz et al., 2019). It uses the Multiphase Optimization Strategy as a methodological framework to optimize the intervention by balancing effectiveness with efficiency, economy, and scalability (Collins, Kugler, & Gwadz, 2016). The MOST framework is conducted over three phases – Preparation, Optimization, and Evaluation – and has been used to optimize a growing number of behavioral prevention

strategies including smoking cessation, school-based drug abuse prevention, HIV-prevention, and adult weight loss (Collins, 2018).

This paper describes the study protocol relating to the Optimization Phase of MOST and follows the SPIRIT guidelines for clinical trials (ClinicalTrials.gov trials registry: NCT03865485;, version 01, issue date: 30. May 2019; see Appendix B for SPIRIT checklist) (Chan et al., 2013). It aims to optimize the PLH Children intervention using a 2 x 2 x 2 cluster randomized full factorial design in order to examine the effectiveness and cost-effectiveness of three intervention components related to program scalability: engagement, length, and fidelity (see Table 1). We will randomly allocate 16 clusters to eight different experimental conditions in each country ($N = 48$ total clusters; 18 participants per cluster, 864 total participants). Six clusters will be allocated to each experimental condition (i.e., 2 per condition in each country) with 108 families per condition ($N = 36$ per country). It is important to note that although there are eight experimental conditions, this study should not be considered an eight-arm randomized controlled trial (RCT). Factorial experiments are critically different from traditional RCTs in that they have the ability to test the effects of multiple intervention components at the same time. Factorial trials are also particularly suitable for disentangling the effects of different components of interventions. They also allow for the examination of interactions between intervention components, which RCTs cannot do. As a result, the purpose of this factorial experiment is to estimate the main effects of the three selected intervention components and interactions between these components, not to compare the eight experimental conditions to each other. Thus, the main effect of each component and interaction effects between components will be based on all of the experimental conditions (Collins, 2018).

Table 1. Experimental conditions (N = 2 clusters per condition per country, 18 participants per cluster).

Experimental condition	Engagement	Length	Fidelity
1	Basic	5 sessions	On-Demand
2	Enhanced	5 sessions	On-Demand
3	Basic	5 sessions	Structured
4	Enhanced	5 sessions	Structured
5	Basic	10 sessions	On-Demand
6	Enhanced	10 sessions	On-Demand
7	Basic	10 sessions	Structured
8	Enhanced	10 sessions	Structured

Study objectives

This study has the following primary research objectives:

1. To examine the efficacy and cost-effectiveness of selected components on primary outcomes (child aggression, dysfunctional parenting, and positive parenting) at post-test (i.e., 6 months after baseline, approximately 3 months post-intervention);

2. To examine the efficacy and cost-effectiveness of selected components on secondary outcomes (internalizing child behavior, child maltreatment, parental psychological distress, and implementation) that are most proximal to each tested component;

We also have the following secondary objectives:

1. To test effects of selected components on primary and secondary at follow-up (i.e., 3 months after post-test, approximately 6 months post-intervention);

2. To explore whether there are any interaction effects between components on primary and secondary outcomes;

3. To conduct exploratory analyses of potential moderators based on baseline characteristics of participating caregivers and children;

4. To identify the most efficient combination of components or component-levels in terms of time, cost, and efficacy to be further tested in a multi-center randomized controlled trial.

Intervention

Parenting for Lifelong Health was initiated through a collaboration among academic institutions, the World Health Organization, and UNICEF to address the need for reducing child mental health disparities and other risks in LMICs (Ward et al., 2014). It aims to develop, evaluate, and disseminate a suite of low-cost, culturally relevant, evidence-based parenting programs across the child development spectrum that can be integrated at scale within existing service delivery systems. Originally developed for families living in low-income communities in South Africa (Lachman et al., 2016), PLH Children targets families with children ages two to nine years has been implemented in 13 countries in sub-Saharan Africa, East Asia, and Southeastern Europe. Grounded in social learning theory principles (Bandura, 1977), the 12-session, group-based intervention contains content similar to other evidence-based parenting programs including relationship building (e.g., child-led play and communicating about emotions), positive reinforcement (e.g., praising and rewarding children; establishing limits through instructions, household rules, and routines), and positive discipline (e.g., ignoring negative attention seeking and demanding behaviors, time-out, and appropriate consequences) (Leijten et al., 2018).

PLH Children has demonstrated promising effects on improving child and parenting outcomes in a series of randomized controlled trials (RCTs) in South Africa (Lachman, Cluver, et al., 2017; Ward et al., 2019) and the Philippines (Lachman et al., forthcoming). Nonetheless, the current intervention package may require further enhancement or modification in order to maximize its effectiveness and scalability. Implementing agencies engaged in the routine service delivery of the program have identified a number of components that may limit its overall scalability. These include the overall length of the program, the provision of incentives for participation and engagement, and the intensity of training and supervision of facilitators (Clowns Without Borders South Africa, 2018). Qualitative interviews of service providers, facilitators, and participating families have also identified similar barriers to implementation, especially in LMICs where there are limited human and financial resources (Alampay et al., 2018; Doubt et al., 2018; Wessels & Ward, 2015).

During the first phase of RISE in 2018, we conducted surface adaptation and a pilot study of intervention feasibility when delivered in youth-friendly health centers (Republic of Moldova), kindergartens, and primary schools (North Macedonia and Romania) (Frantz et al., 2019). Although implementation varied across countries (e.g., a 6-session version of the program was piloted in Romania), results showed significant reductions in child behavior problems (Cohen's d ranged from -1.15 for older children to -1.26 for younger children), as well as reduced child maltreatment (d = -0.82), reduced harsh parenting (d = -0.91), improved positive parenting (d = 0.82), and improved parental mental health (d = 0.50). Based on results from the pilot study, the following components were identified for testing during the factorial experiment: program length, engagement boosters, and fidelity boosters (see Conceptual Model in Figure 1). All program protocols are manualized and freely available on the RISE website (www.rise-plh.eu).
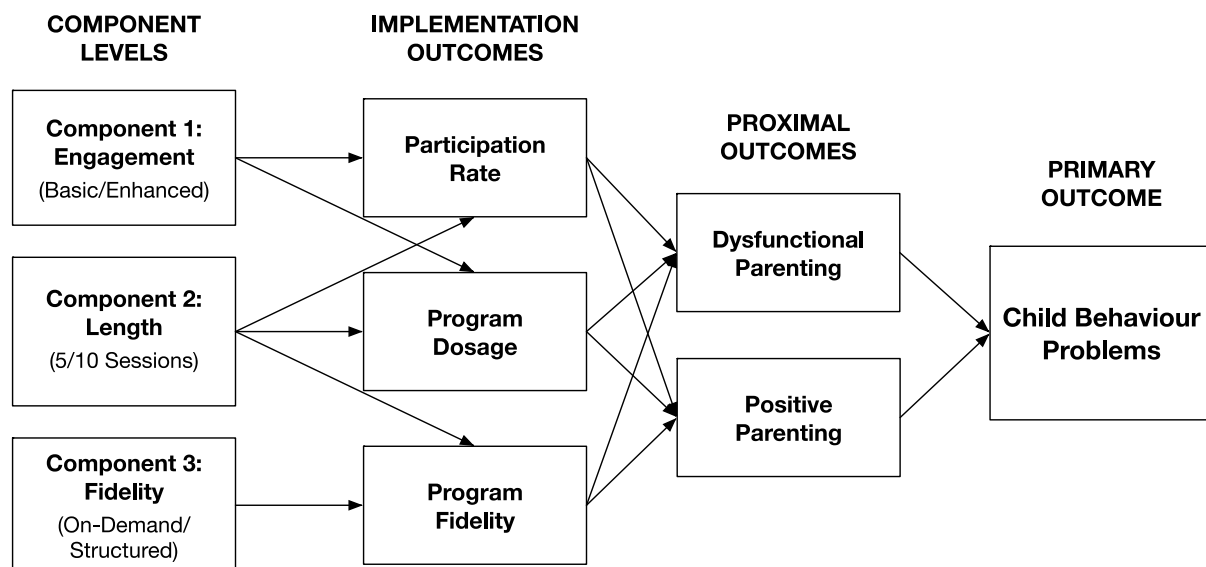
Figure 1. Conceptual model for PLH Children. Participation rate = Percentage of the program received. Program dosage = Number of sessions attended. Program fidelity = Percentage of prescribed delivery and competence adherence.

Components

The following components will be tested in this factorial experiment: A) engagement, B) length, and C) fidelity.

Component A: Engagement

Program dosage, or exposure, has been linked to intervention effectiveness in numerous studies of parenting programs (Nix, Bierman, & McMahon, 2009; Shenderovich et al., 2018; Weeland et al., 2017). Many parenting programs utilize a variety of engagement boosters, or incentives, to increase participant engagement (Axford, Lehtonen, Kaoukji, Tobin, & Berry, 2012; Furlong & McGilloway, 2014; Koerting et al., 2013). For instance, text message boosters may be effective in promoting both attendance in group sessions and the application of parenting skills at home (Murray, Woodruff, Moon, & Finney, 2015). On the other hand, whilst these boosters may increase program engagement and effectiveness, the additional financial and human

resources required to implement them may not be the most feasible and cost-effective approach.

This study aims to test the effectiveness and cost-effectiveness of engagement by offering half of the participants a basic engagement package and the other half an enhanced package that was part of the original intervention. The basic package consists of childcare and transportation support for those who need it as well as a simple snack (i.e., tea/coffee and fruit/biscuits). In addition to the basic support, the enhanced engagement package also consists of food parcels for each participant at each session, a raffle prize awarded at the end of each session, and rewards for attending 80% of the program. The enhanced engagement package also includes a communication booster involving five 10-minute phone consultations in between each session and 28 text message reminders (N = 3-6 messages per session depending on the number of sessions; see Table 2).

Table 2. Examples of text message sent as part of enhanced engagement package.

Construct	Example
Reminder of core lesson	Hi [Name of Parent]! Thank you for coming to the session yesterday. We were so happy to see you! Remember that spending One-on-One Time with your child is one of the best gifts you can give him/her. Quality time is precious! Good luck with your home activities! Thank you, *[Facilitator Name]*
Engagement in home activities	Hello! Remember that it is what you do at home that makes the difference! Keep spending 5 minutes a day in One-on-One Time with your child. Let your child take the lead! Describe your child's actions and feelings! If you are having any challenges, note them down, and we will discuss them at the next session. Thank you, *[Facilitator Name]*

Participation	Hello! Please remember that Session 4 of [Insert Name of Program] will take place on [insert day and time]. We will be learning how to use simple rewards for behaviors that are especially difficult for your child to learn. We look forward to seeing you there! Thank you, *[Facilitator Name]*

Component B: Length

Program length, which is directly linked to dosage, may also have an impact on intervention effectiveness and cost (Barlow, Bergman, Kornør, Wei, & Bennett, 2016; Tully & Hunt, 2016). This study will test long and short versions of the PLH Children program in order to empirically examine whether program length has an effect on primary and secondary outcomes related to child mental health problems. During the feasibility pilot phase of RISE, results showed that the original 12-session version and a condensed 6-session version had positive intervention effects, albeit these results were from different countries. However, qualitative findings indicated that the 12-session program was too burdensome to fit within existing service delivery systems in Southeastern Europe (Frantz et al., 2019). During subsequent program revision, the long version of the program was reduced to 10 group sessions. Thus, in the factorial experiment, half of the participants will receive five group sessions (i.e., 10 hours of program delivery) and half of the participants will receive 10 group sessions (i.e., 20 hours of program delivery). Both short and long versions will be delivered over 10 weeks, with the 5-session version of the program delivered every other week, and the 10-session version delivered every week. Although this may introduce a potential confounder between session length and frequency of delivery, we chose this design in order to assure equal amount of time between baseline assessments, program delivery, and follow-up assessments. Both sessions

will also cover similar core topics though the 10-session version will have more content per topic (Table 3).

Table 3. Content for 5-session and 10-session versions of PLH Children.

Theme	5-Session Program Content	10-Session Program Content
Relationship building	Session 1: One-on-One Time and Say What You See	Session 1: One-on-One Time
		Session 2: Say What You See
Positive reinforcement	Session 2: Praise and Rewards	Session 3: Praise
		Session 4: Simple Rewards
Limit setting	Session 3: Instructions, Redirect, Rules, and Routines	Session 5: Instructions and Redirect
		Session 6: Rules and Routines
Effective discipline	Session 4: Ignore and Consequences	Session 7: Ignore
		Session 8: Consequences for Noncompliance
		Session 9: Consequences for Rule Breaking
Closing	Session 5: Reflection and Moving On	Session 10: Reflection and Moving On

Component C: Fidelity

The level of supervision provided to program facilitators may have an effect on competence adherence, thus indirectly impacting intervention effectiveness (Fagan, Hanson, Hawkins, & Arthur, 2008). There is limited research regarding what level of supervision is necessary to achieve program effectiveness, and whether this level constitutes a cost-effective approach (Rakovshik, McManus, Vazquez-Montes, Muse, & Ougrin, 2016). The RISE project will compare two different levels of supervision. Half of the facilitators embedded in participating clusters will receive five structured supervision sessions using video-feedback coaching with a trained coach (i.e., structured supervision), while the other half of the facilitators will receive supervision from trained coaches only upon request (i.e., on-demand supervision). All facilitators will receive the same five-day training from a PLH trainer regardless of allocation. Coaches will receive a two-day training and five online mentorship sessions from a PLH trainer using the same video-feedback techniques used in the supervision sessions.

Hypotheses

In order to test the effectiveness and cost-effectiveness of each component, this study will examine the following hypotheses based on the aforementioned conceptual model:

1. Engagement: We hypothesize that the enhanced engagement package compared to a basic engagement package will result in higher participation rates of parents (i.e., attendance). Higher participation rates will, in turn, result in improvements in primary and secondary outcomes (via indirect effects).

2. Length: We hypothesize that those receiving the shorter program will have higher participation rates than those receiving the longer program. However, groups receiving 10

sessions will have higher dosage compared to the condition with five sessions, and therefore, we expect no difference on outcomes.

3. Fidelity: We hypothesize that structured supervision will result in higher program fidelity, which will yield larger intervention effects on primary and secondary outcomes than supervision on-demand.

4. Higher baseline levels of parental mental health symptoms and problems in the family environment will be associated with greater change on primary and secondary outcomes. Other moderators of intervention effects, such as parental age, ethnicity, and gender and age of the child, will be examined on an exploratory basis.

Additional exploratory hypotheses

5. We hypothesize that there will be an interaction effect between the engagement and length components. Program length will interact with engagement and lead to greater change in primary and secondary outcomes when both components are on high level. In addition, we expect that the main effect of engagement on retention and participation rates in Hypothesis 2 will remain regardless of program length.

6. We hypothesize that there will be an interaction effect between fidelity and engagement components, such that higher levels of fidelity and engagement components will result in higher retention and participation rates than either component alone. Higher retention and participation rates will in turn be associated with greater change in primary and other secondary outcomes.

7. There will be an interaction effect between program length and fidelity in which conditions receiving ten sessions in combination with structured supervision will result in a larger effect on primary and secondary outcomes than either component alone.

Participants and eligibility criteria

Recruitment will target low-income communities in order to recruit socioeconomically disadvantaged families with children who have higher risk of elevated child mental health problems. Eligible clusters in these communities will be youth-friendly health centers (Republic of Moldova), kindergartens, and primary schools (North Macedonia and Romania). Each participating center will identify two facilitators to deliver the intervention, with the exception of North Macedonia which will have two clusters per pair of facilitators ($N = 80$ facilitators; 32 each in Republic of Moldova and Romania, 16 in North Macedonia where facilitators will deliver the program twice). Eligible facilitators will 1) be age 18 or older, 2) have participated in a PLH Children facilitator training workshop, 3) are available to deliver the entire PLH Children program, and 4) have provided informed consent to participate in the study. Additionally, program coaches will be selected from personnel who have previously implemented the program during the first phase of RISE ($N = 12$; 3 in North Macedonia, 4 in Republic of Moldova, and 6 in Romania). These coaches will be trained and supervised remotely by a mentor who was one of the developers of PLH Children.

Eligible adult caregivers within each cluster will 1) be 18 years or older, 2) identify as the primary caregiver responsible for the care of a child between the ages of two and nine years, 3) live in the same household as the target child for at least four nights a week in the previous month, 4) provide informed consent to participate in the full study, and 5) report that the child they choose to focus on for the program has subclinical levels of child behavior problems based on scores of ten or above on the Child and Adolescent Behavior Inventory oppositional defiant disorder subscale (8 items) (Burns, Lee, Servera, McBurnett, & Becker, 2015). Since this study is aimed at the prevention rather than treatment of child mental health problems, we will use a lower threshold for behavior problems than the original trial of PLH Children in South Africa, which targeted families with children with clinical levels of behavior problems based on the

Eyberg Child Behavior Inventory (Ward et al., 2019). Nonetheless, families with children with clinical levels of behavior problems will also be included. Exclusion criteria for adult caregivers include any adult that 1) exhibits acute mental health problems, 2) has a severe learning disability, or 3) has been referred to child protection services due to child abuse. Excluded adults will be given self-referral forms for available social services and assistance in accessing these services if requested.

Power calculations

Power calculations for the 2^3 clustered factorial design were estimated using STATA. Following recommendations for component selection by Collins et al., 2014 and Watkins et al., 2016, a sample size of 480 was determined as necessary to detect a small effect size of $d =$ .20, accounting for clustering (ICC = 0.05), and 80% power at alpha = .10 per intervention component. Given the intention-to-treat design using full information maximum likelihood estimation to account for any missing data due to study dropout, we will not reduce the final estimated sample size at post-intervention assessment. However, to account for dropout prior to study allocation, the risk of empty clusters, and potentially higher ICCs within country sites, we will oversample N = 18 per cluster with a total sample size of 864. This will enable us to account for an ICC of 0.10 and still detect a minimal effect size of 0.20 (i.e., cluster size = 18; ICC = .10, β = .80, α = .10, N =864). Power calculations will not take into consideration subgroup analyses as these will be treated as exploratory.

Randomization

Cluster randomization of participating centers (N = 48) will be conducted at a centralized location in Klagenfurt in order to assure allocation concealment until the moment of cluster assignment. Country-level research managers will send lists of recruited clusters to Klagenfurt prior to randomization. We will use an randomization website to generate random numbers for allocation of clusters to conditions (https://www.randomizer.org/#randomize). Cluster randomization will be stratified by country-site, with two centers, or parent groups, allocated to one of the eight experimental conditions in each country. Sixteen pairs of facilitators will be nested within each site prior to randomization in Republic of Moldova and Romania. In North Macedonia, eight pairs of facilitators will be nested within sites for randomization of the first set of eight clusters and non-nested for the randomization of the second set of eight clusters (each facilitator pair will administer the program twice to the same experimental condition). This discrepancy is due to the recruitment of only 16 facilitators in North Macedonia, whereas 32 facilitators will be recruited in both Moldova and Romania. Allocation of clusters will be sent back to the research managers in the Republic of Moldova, Romania, and Northern Macedonia after randomization.

Blinding

Implementing partners in each country site will notify the participating families of their allocation status (based on clusters) after baseline data collection is completed in each cluster to ensure that participants are blind to allocation during the initial assessment. Research assistants conducting data assessments will also be blind to allocation in order to minimize assessment bias. Blinding after baseline assessments will not be possible for service providers and participants due to their involvement in program implementation. However, participants

will not be informed about the range of possible conditions for allocation. Contamination will be monitored throughout the study.

Participant timeline

The participant timeline is summarized in the study diagram (Figure 2). Potential caregivers will be recruited after cluster randomization based on targeted/purposive sampling in each country site (January 2019). Recruitment will rely predominantly on in-country implementation partners to identify eligible caregivers. The research team will approach potential participants after parents have given initial consent for a referral by implementation partners. Parents will then be invited by research coordinators to participate in the study via telephone calls, letters, or in-person. Each participant will be screened for eligibility during this initial contact. Recruitment will continue until full study enrolment of 18 caregivers per cluster is achieved (February to April 2019). If necessary, additional recruitment will include invitations by implementing partners to community groups and leaders, as well as "word-of-mouth" referrals in the community via chain sampling methods. Participants will then provide full consent and be assessed at baseline by trained data collectors (i.e., immediately after cluster randomization, March 2019, see Appendix A. for Information Sheet and Consent Form). Those who complete baseline assessments will be enrolled into the program and contacted by group facilitators to arrange individual consultations at implementation centers. They will then receive the PLH Children program (April to July 2019). Post-test assessments will be conducted by data collectors approximately seven months after baseline (September to October 2019), with follow-up assessments approximately three months after post-assessments (January to February 2020).
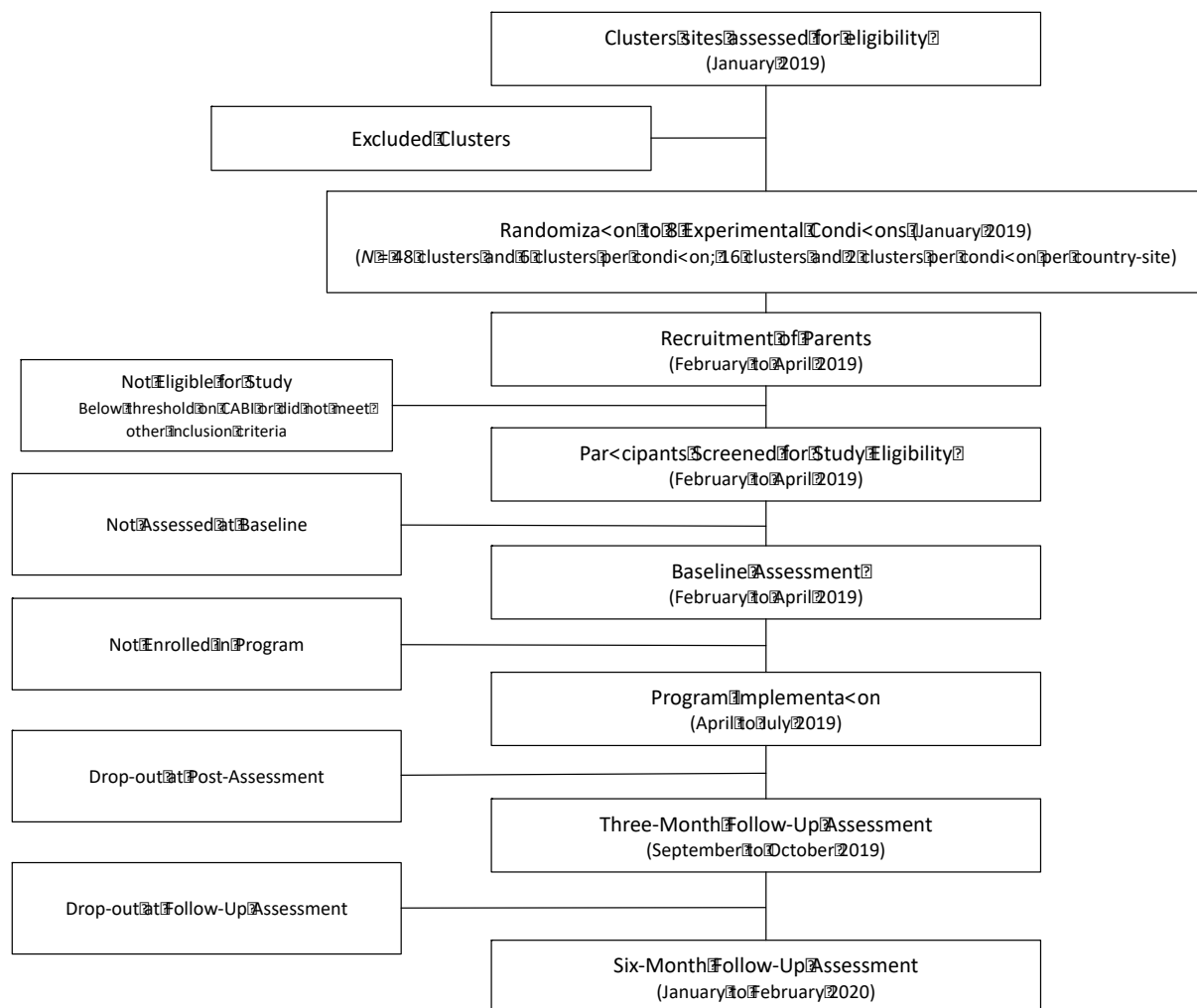
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                    ┌─────────────────────────────────────┐
                    │  Clusters sites assessed for eligibility │
                    │            (January 2019)              │
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                                     │
    ┌──────────────────────┐         │
    │   Excluded Clusters   │─────────┤
    └──────────────────────┘         │
                    ┌─────────────────────────────────────────────────────────────┐
                    │  Randomization to 8 Experimental Conditions (January 2019)    │
                    │ (N = 48 clusters and 6 clusters per condition; 16 clusters and│
                    │        2 clusters per condition per country-site)             │
                    └─────────────────────────────────────────────────────────────┘
                                     │
                    ┌─────────────────────────────────────┐
                    │      Recruitment of Parents           │
                    │      (February to April 2019)         │
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                                     │
  ┌──────────────────────────────┐  │
  │      Not Eligible for Study    │  │
  │ Below threshold on CABI or did │──┤
  │  not meet other inclusion      │  │
  │           criteria             │  │
  └──────────────────────────────┘  │
                    ┌─────────────────────────────────────┐
                    │ Participants Screened for Study Eligibility │
                    │      (February to April 2019)         │
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  │    Not Assessed at Baseline    │──┤
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                    │       Baseline Assessment             │
                    │      (February to April 2019)         │
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  │     Not Enrolled in Program    │──┤
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                    ┌─────────────────────────────────────┐
                    │       Program Implementation          │
                    │        (April to July 2019)           │
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  │   Drop-out at Post-Assessment  │──┤
  └──────────────────────────────┘  │
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                    │   Three-Month Follow-Up Assessment    │
                    │     (September to October 2019)       │
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                                     │
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  │ Drop-out at Follow-Up Assessment│─┤
  └──────────────────────────────┘  │
                    ┌─────────────────────────────────────┐
                    │    Six-Month Follow-Up Assessment     │
                    │     (January to February 2020)        │
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Figure 2. Study diagram.

Outcomes

Primary outcomes

This study will assess three primary outcomes: *child externalizing behavior*, *dysfunctional parenting,* and *positive parenting*. *Child externalizing behavior* will be assessed using parent-report of the Child Behavior Checklist (CBCL) 1 ½ to 5 and 6 to 18 subscales on Aggressive behavior (19 items and 18 items, respectively) (Achenbach & Ruffle, 2000). Although this study originally intended on using the full CBCL externalizing subscale, it had poor psychometric properties when tested during the pilot study in comparison to the Aggressive behavior subscale (i.e., Cronbach alphas were 0.43 and 0.65 for externalizing behavior versus

0.86 and 0.87 for aggressive behavior). *Dysfunctional parenting* will be measured using a shortened version of the Parenting Scale (21 items)(Arnold, O'Leary, Wolff, & Acker, 1993). Although normally assessing Laxness, Over-reactivity, and Verbosity, this study excluded the Verbosity subscale due to poor performance in the pilot study, which was consistent with numerous other studies evaluating this subscale's psychometric properties (Pritchett et al., 2010; Rhoades & O'Leary, 2007). *Positive parenting* will be assessed using the Parenting of Young Children Scale (21 items) (McEachern et al., 2011).

Secondary outcomes

Parent-report of secondary outcomes include *internalizing child behavior* (CBCL 1 ½ -5 and 6-18 subscales with 31 and 32 items respectively) (Achenbach & Ruffle, 2000); *overall child maltreatment* as well as *physical abuse, emotional abuse, and neglect* (based on International Child Abuse Screening Tool-Intervention, 16 items); and *parental psychological distress* (Depression, Anxiety, and Stress Scale, 21 items).

The study will also examine the following secondary outcomes based on the RE-AIM framework for implementation and linked to each tested component level (Glasgow, Vogt, & Boles, 1999). *Participation rates* will be collected by program facilitators using registration forms and be defined as the percentage of total sessions attended. *Program dosage* will be defined as the number of sessions attended as well as dosage in hours. *Program fidelity* will be based on a ratio of activities delivered to activities prescribed in the facilitator manual using facilitator self-report activity checklists. Finally, *competence adherence* will be based on video-coding of program delivery using the PLH Facilitator Assessment Tool (PLH-FAT) (Lachman, Booij, et al., 2017). Seven standard behavior categories are grouped into two scales based on the core activities (28 items) and process skills (19 items) as outlined in the program

manual (Lachman, Hutchings, et al., 2017). Videos will be coded by trained coaches who will not be blind to allocation.

Other pre-specified outcomes

Other pre-specified outcomes linked to increased risk of child behavior problems include *parenting stress* (Parenting Stress Scale, 18 items); *intimate partner violence victimization and perpetration* (Conflict Tactics Scale, 29 items); *parental relationship quality* (Couple Satisfaction Index, 4 items), and *child quality of life* (Child Health Utility 9D, 9 items).

Cost outcomes

Cost to outcomes will be collected using cost diaries completed by relevant staff (i.e., coordinators, mentors, trainers, coaches, and facilitators). Costs will include time and money spent on preparation, training, program delivery, and coordination. These will be broken down by experimental condition in order to assess the costs of each component (Table 4).

Table 4. Components for cost analysis.

Component	System cost	Participant cost
Training (all conditions)	Facilitator, coach, mentor, trainer, & coordinator, venue rental, materials, meals	None
Engagement booster	Facilitator & coordinator, text messages, phone consultations, food parcels, raffle prizes, awards for attendance	Time for phone consultations
Program length	Facilitator & coordinator, venue rental, childcare, transport support for individual consultations & group sessions	Time for individual consultations and group sessions

Fidelity booster	Facilitator, coach, mentor, coordinator; materials for video monitoring	None

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Data collection

Data assessors will be local research assistants who will receive intensive training in ethics, informed consent, and interviewing techniques by the study investigators. All questionnaires were translated into local languages (i.e., Macedonian and Romanian) and back-translated into English to verify accuracy. Assessors will administer questionnaires with electronic tablets using the open-source software platform, Open Data Kit. This method of data collection has been pilot-tested during the previous feasibility study with high acceptability to respondents. Open Data Kit supports multiple languages, and so can include English as well as local languages. Although ongoing studies report exceptionally high acceptability of using electronic tablets in the participating countries, if any participants are unable or uncomfortable with the use of tablets, a paper-and-pen interviewer-assisted questionnaire will also be available. In addition, the study will administer sensitive items on the questionnaires using audio computer-assisted self-interviewing (CASI) techniques. Audio-CASI techniques have been shown to be especially effective in increasing participant willingness to disclose highly stigmatized activities or experiences (Davies, 2005; Phillips, Gomez, Boily, & Garnett, 2010). In particular, audio-CASI may decrease a respondent's anxiety in answering questions face-to-face and thus increase disclosure of sensitive items (i.e., scales measuring child maltreatment and intimate partner violence). Lastly, process data will be collected by program facilitators, coaches, and coordinators in each country site. All participants will receive a food/gift voucher for completing each assessment point (approx. 2-5€).

Data management

All non-electronic data will be stored in a locked filing cabinet at each local country research office. Data collected on electronic tablets will be encrypted as soon as it is finalized (i.e., completed by interviewer) and accessible only by senior research personnel. Tablets will be stored in a locked cabinet at the field office site. These data will be kept for at least 10 years, in accordance with the ethical requirements from the Code of Conduct at the University of Klagenfurt, after which they will be disposed of by the local lead researcher. Electronic data will be transmitted on a weekly basis using a 256-bit encryption via wireless networks to an Open Data Kit server (www.opendatakit) at a central server managed by the University of Klagenfurt's Information Technology Services. Individual datasets from the baseline and follow-up evaluations will be stored separately from the final merged dataset, so that data reference points are available in the data validation process.

Ethical considerations

Ethical approval for this study was granted by the University of Klagenfurt Ethics Board of the Institute of Psychology (Ref: 2018-21), as well as by local country institutional review boards (Republic of Moldova: 43-56/12.04.2018, North Macedonia: 03-1475/2 from 28.03.2019, and Romania: 3322/1.03.2019). Informed consent procedures will be conducted prior to baseline assessments by trained data assessors who will be supervised by local research investigators. Participants will be informed that they have the right to decline to participate and/or to withdraw from the program and/or the research evaluation at any time without it having any effect on their entitlement to other services. Adverse events experienced by the participants over the course of the program will be monitored, including the administration of an event list that supports the project team to classify the occurrence of adverse events. All personal data will be anonymized and assigned a unique research study ID number. Data collection and

management procedures will be monitored centrally by the University of Klagenfurt and locally by each country site research team on a daily basis. An appointed data protection officer will periodically evaluate the data protection and management measures.

Data monitoring

Data safety and monitoring will be conducted by a Data Safety and Monitoring Board (DSMB) consisting of two senior academics from field of child mental health who have extensive experience in implementing complex research studies and research ethics involved in intervention research with families and children. They will review the study procedures and data regarding participant safety, study conduct, and progress, and results. They will also be responsible for making recommendations regarding continuation, termination, or modification of the project.

Analytical strategy

Treatment of missing data

Missingness will be examined prior to analyses and appropriately addressed, via either multiple imputation or full information maximum likelihood estimation, in line with an intention-to-treat protocol for analysis.

Analyses

Analyses will examine the main effect of each component level (e.g., those receiving basic engagement boosters versus those receiving enhanced engagement boosters) and interaction effects between component levels. For pre-post analyses, regression models accounting for clustering and stratification by country will be used and tested in Mplus and SAS. Separate models will be tested using effect coding (Kugler, Dziak, & Trail, 2018; Nahum-Shani & Dziak, 2018). Robust standard errors will also be estimated to adjust for clustering. Hypotheses

related to indirect effects will be tested in Mplus using bootstrapping procedures. For analyses including follow-up data (i.e., pre, post and follow-up change in primary and secondary outcomes), latent growth curve models will be used to model outcome variables over time (Watkins et al., 2016). Main effects will be modeled as a fixed effect, with baseline assessments of each outcome as covariates. Models will also be tested using growth curve models, taking into account adjustments for stratification variables and baseline assessment levels (e.g., including child age as a time-invariant covariate). These analyses will be exploratory as recommended by Watkins et al (2016). We will also examine attendance in the program by using the Complier Average Causal Effect analyses that provides an estimate of causal effects, taking into account attendance (i.e., compliance) and other baseline predictors of attendance (Dunn, Maracy, & Tomenson, 2005; Jo, Ginexi, & Ialongo, 2010).

We will also perform the following multi-group comparisons across sites to detect differences in optimization as a function of country. *Gender*: Child gender will be included as a covariate in the models of outcome. We hypothesize non-significant to small effects on outcomes related to child gender but will also test interactions between gender and other contextual factors (e.g. social, family and cultural characteristics). *Cultural and geographical differences*: This multi-site study will allow for several subgroup analyses related to cultural and society influences as well as economic factors. We will analyze effects of each component based on subgroup analyses across countries (3 sites) and family socio-demographics such as parent/child age and gender, parent educational status, family economic insecurity, parental experience of maltreatment as a child. We will determine whether results can be generalized across subgroups testing for interaction effects or using multi-group analyses across the latent growth curve/multi-level models. It should be cautioned, however, that these subgroup analyses will be treated as exploratory since this study is not powered to detect these interaction effects with

precision. Finally, given that this study is powered as a factorial experiment and not an eight-arm RCT, analyses will not compare different combinations of intervention components.

Cost-effectiveness

Incremental cost effectiveness analyses (CEA) will be conducted from the payer's perspective (excluding participant costs) to assess whether the benefits of each component appear to be worth the added costs. Program costs will be calculated using a micro-costing approach, multiplying resource use by unit costs. For outcome measures, in addition to assessing changes in the CBCL aggression score, the change in quality-adjusted life-years (QALYs) will be studied. Utilities for health-related quality of life for children will be measured using the proxy version of Child Health Utility measure (CHU9D.

Following the work of Bernstein et al., cost effectiveness will be estimated in two passes (2017). First, analyses will examine cost and change in the CBCL aggression score for each of the eight MOST cells, ignoring whether differences are statistically significant. The clearly dominated cells where higher cost is associated with a smaller change in the CBCL aggression score will be dropped. In the second pass, incremental cost effectiveness ratios (ICERs) will be calculated as the incremental change in costs divided by the incremental change in two health outcomes: the CBCL aggression score and QALYs. An ICER of €45,000 or less per QALY gained is reasonably to be considered cost-effective. Bootstrapping techniques will be used to conduct uncertainty analyses to assess variability in our findings from potential sampling bias.

Decision making process

The optimization criteria for this study are set to select only the most effective and cost-effective component levels for inclusion in the subsequent randomized controlled trial. We will

thus use the following selection process. First, we will investigate whether there are differential effects for each component level on primary outcomes. If there is a differential effect for a specific component level, then this component level will be included in the final intervention package. If there are no differential effects on primary outcomes, we will examine potential interaction effects between components to see if a specific component level has a synergistic effect on the effectiveness of another component. For instance, although there may not be any differences on outcomes for conditions receiving five or ten sessions (i.e., Hypothesis 2), the final intervention package would include ten sessions if there were a synergistic interaction effect between engagement boosters and program length resulting in larger effects for conditions receiving ten sessions when combined with enhanced engagement (i.e., Hypothesis 7). If there are no direct or synergistic interaction effects, we will select the more cost-efficient component level (i.e., lower level). If a specific component level has an observed main or synergistic interaction effect on primary outcomes, then we will examine the cost-effectiveness of this component. If it is cost-effective, it will be included in the optimized intervention package; if it is not cost-effective, we will revert to the lower component level (Figure 3).
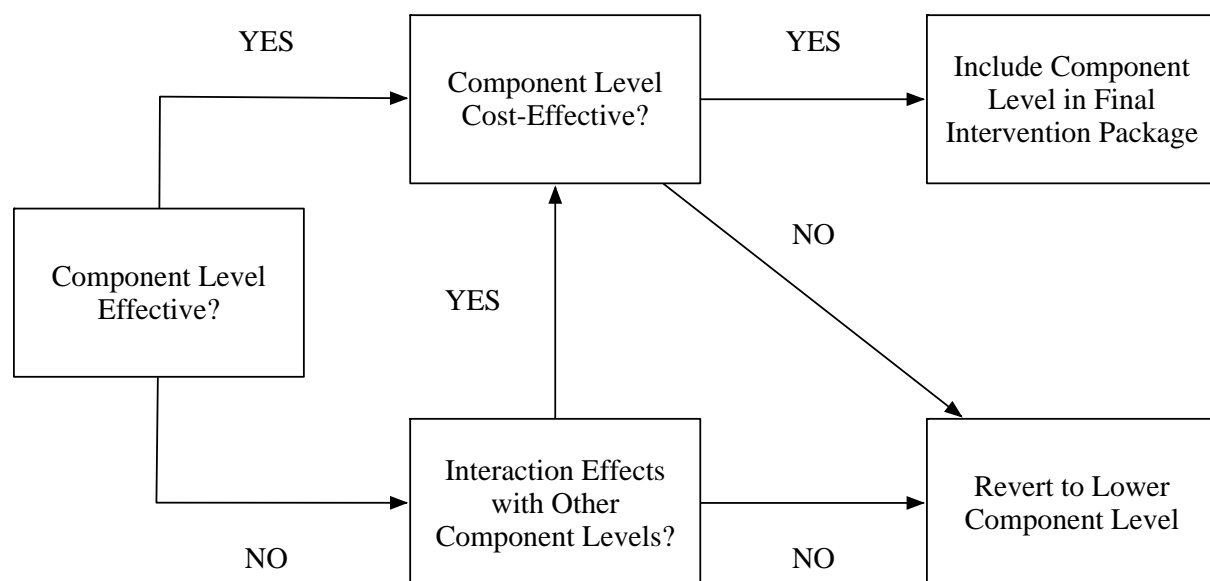
Figure 3. Decision making process for selecting component levels for subsequent trial.

Results will be reported on the RISE website (www.rise-plh.eu). Findings will also be reported at key conferences and summarized in lay-term, one-page policy briefs. We will also make all efforts to provide participants and service providers with brief reports regarding progress and findings from the research (Herth, 1998). Authorship of publications emerging from the study will be decided during a meeting with the Steering Committee (i.e., study PIs) and adhere to the guidelines recommended by the International Committee of Medical Journal Editors (www.icmje.org). All publications and intervention protocols will be available to the public either via open-access journals or an open-access repository following the FAIR (Findable, Accessible, Interoperable, Reusable) principles, Metadata and anonymized data on the aggregate level will be uploaded on Zenodo after publication of the main study results (https://zenodo.org/).

Discussion

This study is the first to our knowledge to use a factorial experiment design to optimize an evidence-based parenting program in low- and middle-income countries. By applying the Multiphase Optimization Strategy framework to reduce child mental health problems in three Southeastern European countries, it aims to test the effectiveness and cost-effectiveness of three intervention component levels linked to program scalability. First, it examines the role of engagement boosters to reduce barriers to program participation by comparing a basic engagement package versus an enhanced engagement package that includes food parcels, incentives for participation, and communication boosters (i.e., text messages and phone consultations). Second, it tests the effect of program length by comparing a five-session version of the program delivered every other week versus a 10-session version delivered weekly. Lastly, it examines the amount of supervision necessary to achieve program fidelity by

comparing structured video-feedback supervision sessions with informal supervision on-demand. Findings will inform the final selection of component levels that are most effective, cost-efficient, and scalable. The effectiveness and cost-effectiveness of this optimized intervention package on reducing child behavior problems will subsequently be tested in a randomized controlled trial in comparison to families receiving a once-off lecture on parenting.

This innovative study has the potential to advance prevention and implementation strategies of parenting programs in order to alleviate the global burden of child mental disorders. Results will provide a valuable contribution to policymaking and practice in terms of addressing child mental health problems in low-resource contexts. Making high-quality programs available to primary caregivers in LMICs is a central path to and an important strategy for addressing mental health disparities in these countries. It is also of vital importance that studies focus on the implementation process, particularly in resource-limited settings, with the ultimate objective to take efficacious programs to scale at a population level. The factorial experiment design allows the investigation of intervention components that are considered important in overcoming barriers to participation and implementation, such as program inaccessibility due to poverty and limited availability professional-level program providers (Durlak & DuPre, 2008). Thus, findings may be applicable to other LMICs that face similar challenges in balancing the demand for implementation at scale with the need to maintain program effectiveness.

Funding

funder was not and will not be involved in the design of the study, the collection, analysis and interpretation of data or the writing of the protocol.

Conflict of Interest

Author Contributions

Protocol Amendments

Interim results for each study phase will be discussed within the RISE research team and changes to the protocol will be made, if necessary. Any subsequent modifications to this protocol need to be approved by all PIs and will be submitted to the IRB and the DSMB for consideration and approval.

Data Statement

Data will be shared among the RISE research team. It is planned to make some anonymized datasets available to the public and other researchers via an open-access repository following the FAIR (Findable, Accessible, Interoperable, Reusable) principles. The research team will ensure that results will be published in open access peer-reviewed journals.

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Appendix A. Information sheet and consent form for parents and caregivers

PIs (researchers): Prof. Adriana Baban, Prof. Xiangming Fang, Prof. Heather Foran, Prof. Frances Gardner, Prof. Nina Heinrichs, Prof. Hutchings, Dr. Jamie Lachman, Dr. Galina Lesco, Prof. Marija Raleva, and Prof. Cathy Ward.

Contact person in your country: [*name and telephone number of respective country P]*

Institutions: Babeș-Bolyai University, Cluj-Napoca (Rumania); Institute for Marriage, Family and Systemic Practice – ALTERNATIVA (FYR Macedonia); Health for Youth Association (Republic of Moldova); Bremen University (Germany); Alpen-Adria-University Klagenfurt (Austria); Bangor University, Wales (United Kingdom); University of Cape Town (South Africa); Georgia State University (USA); University of Oxford (United Kingdom).

Ethics Approval: by the Human Research Ethics Committee of the Alpen-Adria-University Klagenfurt and the Human Research Ethics Commission of [*local institution of respective country*].

PARENTING FOR LIFELONG HEALTH 2-9

Information Sheet for Parents

- **We are asking you to be in a research study.**

- **You do not have to be in the study.**

- **If you say yes, you can quit the study at any time.**

- **Please take as much time as you need to make your choice.**

Why am I asked to be part in this research study?

We want to learn more about how well different versions of a parenting program work. We want to identify the optimal combination of different program components.

The name of the program is *Parenting for Lifelong Health for Young Children, PLH Children*. We are asking people like you who have a child aged 2 to 9 years to help us. A total of 864 parents will be part of the study, 288 in [*add respective country*]. Many other parents have participated in this program in the past.

What if I don't understand something?

- This form may have words you don't understand. Research staff will read it with you, if you like.

- You may ask as many questions as you like before you decide whether you want to be in this study.

- You are free to ask questions at any time before, during, or after you are in the study.

What if I say yes, I want to be in this study?

We first will see if you fit into the study. Therefore, we will ask some questions about your child.

To be part of the study, you need to be a parent or caregiver of a child between the ages of 2 and 9 years whose behavior you are having challenges with. You also have to agree to participate in the parenting program and provide consent in the full study.

If you qualify, we will do these things

- ask about your life, your feelings and your relationship with your child

- read the questions out loud and enter your answers in this electronic tablet

- let you listen to questions by an audio record

- give you a brief form with questions about adverse events in the last week/the last two weeks

- let you skip any question you do not want to answer

- The last section of the interview will be audio recorded but only for parents with a child aged 6 years or older. This is to document how the interviewer is performing and to determine the quality of data collection. If you do not want to be audio recorded, please tell us and we will not record this section.

This will take about 60 minutes.

- We will ask you to participate in the parenting program. The program wants to improve relationships between parents and children. Parents also learn strategies how to deal with their children in challenging situations.

- The program will take place in groups with other families. Two people will deliver the program in community centers / university clinics. Your child will not attend the groups but childcare will be provided if you need it in order to attend the group.

- Before, you will have an individual meeting with your group leader. This person will explain the program in detail to you. During the parent groups, you will do activities and also practice at home. You will only have to do the activities if you wish to.

- During the program, we will use a video to document how well the program is delivered by the facilitators. Further, we will use these videos for our training in order to improve the skills of the facilitators. If you do not want to be in the video, please tell us. We will make sure that you are not in the view of the video camera.

- There are different program activities which might be helpful. In order to have a closer look what works best with families like yours, there will be a randomization process. Randomization means that we will put you into one of the activities by chance. Importantly, you will be in the parenting program, no matter to which group you are assigned.

- We will contact you again after completion of the program. We will ask you the same questions that we will ask you at the beginning. This will take about 60 minutes.

- We will then contact you about 3 months later to ask you the same questions for the last time (approximately 60 minutes). All the interviews will take place at a community center / university clinic, you can decide.

- If you are currently in a relationship, we will also invite your partner/spouse to participate in the study, but they are not required to participate for you to be part of this study.

What if I say no, I do not want to be in this study?

Nothing bad will happen.

What happens if I say yes, but change my mind later?

- You can stop being in the study at any time.

- Nothing bad will happen.

- You do not have to give any reasons.

- If you wish to be taken out of the study, please contact *[add address of respective country PI].*

Who will see the information about me that is collected?

- We will store all of your research records in locked cabinets and secure computer files. Only the research team has access. We will take your name off of any information where this is possible.

- Personal identifying information needed for research purposes (e.g., videos) will be kept for 10 years, after which it will be destroyed. Identifying information such as your name and contact details be destroyed at the end of the study unless you agreed to be contacted in the future in which case we will only keep your name and contact details.

- We will keep all your anonymized as well as personal information confidential as provided by law. The only exception is any risk of possible harm to you or others. If a child is harmed or is at risk for harm, the research team will consult with one another and decide on the best course of action in line with international UNICEF Child protection standards and the Child Protection standards and Policies in your country.

- We will share our study results via the Internet and an open database. Your name or address or other personal identifying information will not appear.

- We will share the results of the study in academic journals, research reports and at conferences. We will take off your name or any other identifying information.

- After the study is finished, you can see the results of the study on our website www.rise-plh.eu.

Will it cost me anything to be in the study?

The study will not cost you anything.

Will I be paid?

You will be receiving a food/gift voucher *[add monetary value (3 – 5 €) for respective county]* after the end of each interview. If you do not miss more than one group session, we will give you an award of worth approximately *[add value for respective county]* Euros.

Will being in this study help me in any way?

- You can participate in the parenting program for free.

- Being in the study may or may not help you, but may help other parents to have a better relationship with their child in the future.

- We do not know whether being in the study and the program activities specifically will help

you individually but we do know that the program activities have helped many other parents like you throughout the world.

What are the risks of being in this study?

- The risks of this study are no more than what happens in everyday life.

- The questions we will ask may make you feel sad, upset or uncomfortable. We will be happy to help you. In that case, we can refer you to support services.

What if I have questions?

- Please call the local head researcher of the study *[enter name and telephone number of respective country P]* if you

  - ✓ have any questions about this study

  - ✓ have questions about your rights

  - ✓ feel you have been injured in any way by being in this study

- You can also call the office that supervises research [*add address and phone number of local Human Research Ethics Commission for the respective country*] if you

  - ✓ have questions about this study

  - ✓ have questions about your rights

  - ✓ can't reach the study team

  - ✓ need to speak to someone not directly involved with this study

What should I do if I want to be in the study?

- Sign this form.

- You can wait up to 7 days to decide whether you want to be in the study or not.

- We will give you a copy of this form to keep.

Consent Form for Parents in the optimization study

By agreeing to the project, I am saying

- I understand that joining this study is voluntary.

- I agree to be in the study.

- Someone talked with me about the information in this document and answered all my questions.

- I understand that the information I provide (without any identifying information) may be combined with other families' experiences of similar programs from other countries so that we can understand how they work across the world.

I know that:

- I can stop any and all parts of the study at any time and nothing bad will happen to me.

- I can call the office that supervises research *[enter name and telephone number of respective country P]* if I have any questions about the study or about my rights.

- I do not give up any of my rights by signing this form.

Date: _____

☐ Yes, I agree

☐ No, I do not agree

We would like to ask for your permission to contact you in the future to participate in other studies. Would you be willing to be contacted in the future (if you cross "yes" we will keep your name and address in separate files to allow contacting you in the future)?

☐ *Yes* ☐ *No*

Appendix B. SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2 & 6
	2b	All items from the World Health Organization Trial Registration Data Set	NA
Protocol version	3	Date and version identifier	6
Funding	4	Sources and types of financial, material, and other support	5, 30
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1 & 31
	5b	Name and contact information for the trial sponsor	30
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	30

| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | NA |

Introductio

n

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-5
	6b	Explanation for choice of comparators	NA
Objectives	7	Specific objectives or hypotheses	6-7, 14-16
Trial design	8	Description of trial design including type of trial (e.g., parallel group, crossover, factorial, single group), allocation ratio, and framework (e.g., superiority, equivalence, noninferiority, exploratory)	5-6, 19

Methods: Participants, interventions, and outcomes

| Study setting | 9 | Description of study settings (e.g., community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained | 16 |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (e.g., surgeons, psychotherapists) | 16-17 |

Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-14
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (e.g., drug dose change in response to harms, participant request, or improving/worsening disease)	24
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (e.g., drug tablet return, laboratory tests)	23-25
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NA
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (e.g., systolic blood pressure), analysis metric (e.g., change from baseline, final value, time to event), method of aggregation (e.g., median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	20-22
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (Figure 2)	19-20
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	17

| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | 16-17 |

Methods: Assignment of interventions (for controlled trials)

Allocation:

| Sequence generation | 16a | Method of generating the allocation sequence (e.g., computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (e.g., blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | 18 |

| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (e.g., central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | 19 |

| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | 19 |

| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (e.g., trial participants, care providers, outcome assessors, data analysts), and how | 19 |

| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | 19 |

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (e.g., duplicate measurements, training of assessors) and a description of study instruments (e.g., questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	20-23
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	23-24
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (e.g., double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	24
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	25-27
	20b	Methods for any additional analyses (e.g., subgroup and adjusted analyses)	27
	20c	Definition of analysis population relating to protocol non-adherence (e.g., as randomized analysis), and any statistical methods to handle missing data (e.g., multiple imputation)	25

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	24-25
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	25
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	24
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA

Ethics and dissemination

| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | 24 |
| Protocol amendments | 25 | Plans for communicating important protocol modifications (e.g., changes to eligibility criteria, outcomes, analyses) to relevant parties (e.g., investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | 32 |

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	16, 19, 24-25
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	24-25
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	31
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	32
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (e.g., via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	29
	31b	Authorship eligibility guidelines and any intended use of professional writers	29
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	29

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.