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Evaluating Pictorial support in Person-centred Care for Children (PicPecc): a protocol for a crossover design study.

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2
3 **Title page**
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5 **Evaluating Pictorial support in Person-centred Care for Children (PicPecc): a protocol**
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7 **for a crossover design study.**
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Abstract

Introduction: This study protocol outlines the evaluation of the digital tool Pictorial support in Person-centred Care for Children (PicPecc) used by children with cancer aged 5-17 years, who undergo two high-dose methotrexate treatments, to self-report symptoms. The platform follows principles of Universal Design using pictorial support to provide accessibility for all children regardless of communication or language challenges and thus facilitating international comparison.

Methods and analysis: Both effect and process evaluations will be conducted. A crossover design will be used to measure the effect/outcome, and a mixed-methods design will be used to measure the process/implementation.

The primary outcome in the effect evaluation will be self-reported distress. Secondary outcomes will be: stress levels monitored via neuropeptides, neurosteroids and peripheral steroids indicated in plasma blood samples; frequency of in-app estimation of high levels of distress by the children; children's use of analgesic medicine; and person-centeredness evaluated via the questionnaire Visual CARE Measure.

For the process evaluation, qualitative interviews will be carried out with children with cancer, their legal guardians and case-related healthcare professionals. These interviews will address experiences with PicPecc in terms of feasibility and frequency of use from the child's perspective and value to the caseworker. Interview transcripts will be analysed using an interpretive description methodology.

Ethics and dissemination: Ethical approval was obtained from the Swedish Ethical Review Authority (ref 2019-02392; 2020-02601). Children, legal guardians, healthcare professionals, policymaking and research stakeholders will be involved in all stages of the research process according to Medical Research Council's guidelines. Research findings will be presented at international cancer and paediatric conferences and publish in scientific journals.

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3 *Trial registration:* The trial is registered at ClinicalTrials.gov: NCT04433650
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8 **Keywords:** Clinical trial; Paediatric oncology; Pain management; Qualitative research
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For peer review only

Strengths and limitations of this study

- The digital tool was designed based on person-centred and universal design principles permitting equality of access.
- A person-centred framework is used to evaluate outcomes.
- A child-centred pictorially supported communication device is used to self-report distress from the age of 5 years.
- The study evaluates a complex intervention with a combination of subjective and objective measures.
- Objective evidence of stress is monitored via blood plasma.
- The process evaluation will give additional information for future usage based on the frequency and feasibility of use.

Introduction

Children with cancer struggle with several physical and emotional symptoms. Their ability to communicate these symptoms is dependent on various factors, such as age, maturity, diagnosis, cognitive status, psychological status, language ability, and cultural background, as well as situational aspects. Alleviating distress caused by cancer is beneficial for both children, their families and healthcare professionals¹. Symptom identification and communicative support can enable symptom relief with the potential to reduce distress and alleviate suffering for the child, and will also improve quality of the care¹.

Person-centred care for children

Person-centred care is founded in ethics and based on the assumption that every person has resources that should be used in the care situation; being human is about having capabilities. This can be referred to Homo capax², i.e., a person with capabilities and vulnerabilities, and who is considered responsible for her/his actions in relationships with others³. There is no gold standard definition of person-centred care and the exploration of the concept has emphasized many different aspects and different definitions. In this project, the definition of person-centred paediatric care is based on three key concepts of partnership, narrative and documentation; generating a co-created partnership, and safeguarding the partnership through documenting the child's narrative, preferences and participation^{4 5}.

The project is founded on the ethical principles put forward by the French philosopher Paul Ricœur which aims for the good life, with and for others, with equitable and unbiased institutions⁶. In this regard a person-centred approach with a child perspective includes the idea of what is best for the child but also acknowledges the self-determination of the child. Decisions are therefore made that balance these concepts; that is, not solely from an adult's

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3 view of the child's needs nor solely from the perspective of the children themselves. Instead,
4
5 the desired solution is to combine the child's experience, the perspectives of legal guardians
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7 and significant others and the healthcare professionals. Within this balance, however, it is
8
9 important to always prioritize the children's best interests in an attempt to optimize their
10
11 well-being⁷.
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17 To initiate a person-centred approach for paediatric care is to elucidate, listen to and affirm
18
19 the child's narrative. Assessments of symptoms are essential in symptom relief for children
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21 with cancer, and self-reports are the gold standard for measuring symptoms^{8 9}.
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26 Children's own voices and self-reports are necessary to our understanding of the issues facing
27
28 children if we are to reach the goal of symptom relief⁷. Children with cancer – like all
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30 children – have the right to actively take part in decisions regarding their health. In order to
31
32 achieve this, they need support to communicate issues related to their symptoms. For such a
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34 system to work well in their everyday lives, symptom communication will largely rely on
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36 identification of symptoms, and communication skills and pathways to present this
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38 information in a timely and appropriate manner within their healthcare management¹⁰.
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44 *Universal design*

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46 Healthcare professionals often tend to use language that is too complex for children to
47
48 understand. Children can therefore be said to be 'communication vulnerable'¹¹, depending on
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50 their level of health literacy, potential cognitive or communicative disabilities, age, language
51
52 level or competency in the majority language¹². The Convention on the Rights of Persons
53
54 with Disabilities (CRPD) proposed the idea of 'universal design' to the design of products,
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3 environments, programmes and services so that they would be usable for all people, to the
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5 greatest extent possible, without the need for adaptation or specialised knowledge¹³.
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10 The application of new digital technologies using pictorial supported communication may
11 assist communication vulnerable children in healthcare to more effectively self-report and
12 communicate with others about their symptoms, overcoming their, and possibly their
13 families' communication difficulties. Pictorial communication support may foster closer
14 relationships, trust and more open communication between families and healthcare
15 professionals¹⁴.
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26 *Self-assessment tools*

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28 The development of assessment tools for children to self-report pain started in the 1980s,
29 with the widespread implementation of these tools in the 1990s¹⁵. However, children's self-
30 reports have been shown to still fail to impact healthcare, and there is a need for innovative
31 ideas that support the implementation of these assessment tools in clinical practice^{16 17}.
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37 Enabling children with cancer to self-report their symptoms may help them to understand
38 their condition better and thereby better cope with their illness. Communicating symptoms in
39 an effective way that can quickly alert healthcare professionals to their discomfort is an
40 empowering process that will make them feel secure in knowing that they have strategies that
41 give them the possibility to communicate with somebody who will assist them to achieve
42 symptom relief¹⁸.
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53 Although validated patient self-report instruments exist for some symptoms healthcare
54 professionals seldom use these in clinical practice ¹⁷ furthermore most paediatric conditions
55 lack a validated symptom assessment tools. What is missing from the clinical toolbox is an
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3 instrument that assesses the intensity of symptoms in a simple, valid and reliable way¹⁹. One
4 of few symptoms that is assessed in clinical practice is pain intensity. Smeland et al. (2018)
5 found that, overall, pain was assessed using validated tools in 19% of the children in post
6 anaesthesia care; this fell to 9% in children aged <5 years old¹⁷. An explanation for this could
7 be either that these instruments do not exist or that they are difficult to use, interpret or
8 unreliable. Healthcare professionals prefer to rely on personal judgement and experience
9 with the patient and family²⁰ and therefore the measurement process must contribute to this
10 and not try to replace it. The use of an instrument that focuses on a single symptom, for
11 example pain intensity, does not adequately capture the overall experience of the child and
12 can be considered a restrictive application. Novel assessment tools that give a broader
13 description of symptoms are therefore needed in order that the child can fully communicate
14 their experience.

33 *Distress in children*

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35 The term "distress" refers to a multifactorial unpleasant emotional experience that can be
36 described as a combination of fear, anxiety, and pain²¹. The relationships between these
37 factors are complex, and the experience of distress is based on interactions between
38 "genetically linked behaviour patterns, temperamental predispositions, normal developmental
39 fears, parental psychopathology, and discrete learning experiences"²². Distress in this study is
40 defined as an experiential response and sensation of the mind associated with negative
41 emotions that appear when a situation is fearful or impossible to manage from the perspective
42 of the child. Distress can be a consequence of insufficient symptom relief, and self-reported
43 distress is a global assessment that reflects the child's experience of the success of symptom
44 relief. It is important to evaluate the distress in children undergoing cancer treatment and to
45 find strategies for the measurements of symptoms/emotions that are reliable and valid for this
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3 purpose. It is known that acute stress activates the hypothalamic–pituitary–adrenal (HPA)
4 axis and the sympathetic nervous system (SNS), as well as the hypothalamic–pituitary–
5 gonadal (HPG) axis²³⁻²⁵. For example, plasma cortisol concentration is an established stress
6 (energy mobilization) indicator that is known to react within minutes after the onset of stress
7 exposure. Estradiol is on the other hand an anabolic hormone, which protects against adverse
8 effects of stress.
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19 *The medical scenario within which PicPecc will be tested*

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21 The drugs used to treat children with cancer can lead to several negative side-effects, e.g.,
22 children undergoing cancer treatment frequently report nausea and vomiting and other kind of
23 distress²⁶. One of the drugs that is used in cancer treatment is methotrexate which is one of
24 the most effective medications in the treatment of acute lymphoblastic leukaemia (ALL) in
25 children²⁷. High-dose methotrexate is used world-wide and has been included as part of the
26 Nordic Society for Paediatric Haematology and Oncology acute lymphoblastic leukaemia
27 treatment protocols since 1981²⁸. Furthermore, the treatment is given according to a strictly
28 detailed Nordic and European schedules, i.e., clinical conditions have been well established.
29 For these reasons, treatment with high-dose methotrexate has been chosen as the medical
30 context within which the effect of the use of PicPecc tool will be evaluated from a person-
31 centred perspective.
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49 The primary aim of the project is to investigate whether a person-centred communication
50 intervention through the use of the PicPecc digital communication tool for children
51 undergoing cancer treatment decrease the children's distress symptoms. A secondary aim is
52 to investigate the process of implementing person-centred communication through the use of
53 the PicPecc tool.
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3 *Main research question:*
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5 Does adding the PicPecc tool decrease distress (measured on an 11-point numeric rating scale
6 (NRS) (0 [no distress] and 10 [worst possible distress]) in children with cancer, aged 5-17
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8 years, who undergo high-dose methotrexate treatment?
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15 *Secondary research questions:*
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- 17 (i) Does the application of the PicPecc tool, increase person-centredness (measured
18 on VCM (Visual CARE Measure) in children with cancer, aged 5-17 years, who
19 undergo high-dose methotrexate treatment?
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26 (ii) Does the application of the PicPecc tool, alter stakeholders' perspectives on
27 person-centred communication?
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33 *Hypothesis*
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- 35 (i) Children undergoing cancer treatment will experience lower distress levels, when
36 they can report their holistic symptoms in a system created using universal design
37 principles (i.e. the PicPecc tool with pictorial support) than will children with
38 standard healthcare communication opportunities (the primary outcome). In
39 addition to a decrease in self-reported stress levels there will also be a decrease in
40 neuropeptides, neurosteroids and peripheral steroids for stress and pain.
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51 (ii) Person-centred care is enhanced, through enabling children to proactively assess
52 their symptoms from a holistic perspective and communicate these to their
53 healthcare providers within an enhanced communication framework (i.e. using the
54 PicPecc tool).
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Methods and analysis

Study design

The Medical Research Council's key principles and actions for development and evaluation of complex interventions^{29 30} guided the intervention development and the research design. In a hybrid design, both the effects of the intervention and the implementation process will be evaluated³¹. Relevant care situations are selected³² where highly standardized care procedures are used and where there are a range of different situations where children struggle with symptoms. To facilitate the effect evaluation, the children will participate in a crossover design study where they are their own controls (Fig 1). The study design follows the SPENT 2019 checklist for clinical trials³³.

The development of the PicPecc tool follows established guidelines³⁴ and was based on the theoretical framework of person-centred care⁴, on published systematic reviews⁹ and on systematic reviews conducted within the project on assessment tools for nausea³⁵, and anxiety³⁶. Children with cancer, their legal guardians and healthcare professionals have been involved throughout the development process. The study protocol outlined here pertains to the evaluation and implementation phases.

Insert figure 1

Participants and units

Context and setting

In Sweden, approximately 350 children are diagnosed with cancer each year. The treatment of childhood cancer is conducted at six childhood cancer centres and at regional hospitals³⁷.

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3 Three of these childhood cancer centres and a regional hospital in Sweden will participate in
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5 the study.
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10 Selection criteria

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12 Inclusion criteria are children diagnosed with cancer, between 5 and 17 years of age whose
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14 treatment-plan includes at least two treatments of high-dose methotrexate. The child needs to
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16 have a cognitive level of at least five years (i.e., to be able to understand an NRS³⁸). The
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18 child's understanding of an NRS will be tested before inclusion based on a situational
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20 judgment test which involves a realistic, hypothetical scenario about a child who fell from a
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22 tree. The child will be asked to assess pain using the NRS. This situational judgment test has
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24 previously been validated to discriminate positive and negative emotions³⁹. Exclusion criteria
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26 are children 0-4 years, non-completion of consent forms, scheduled to undergo only one
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28 high-dose methotrexate treatment.
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35 The children's legal guardians and the healthcare providers who take care of these children
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37 will be included in the assessment, in addition to the children themselves.
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42 Method of recruitment

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44 The recruitment is planned to start towards the end of 2020. The surveyed children participate
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46 in data collection twice, once as a control (A) and once at the time of symptom reporting and
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48 initial use of the communication tool PicPecc (B) (Fig. 1). Children with cancer aged 5-17
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50 years old, legal guardians and healthcare professionals at three childhood cancer centres and a
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52 regional hospital in Southern Sweden will participate in the study.
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Consent process

Legal guardians of children below 15 years of age with cancer who are scheduled to receive high-dose methotrexate treatments will be informed about the study by a physician or a nurse, included in the research group. The legal guardian will receive written information, and the child will be given text and picture-based information. Child assent is obtained verbally upon consent from a legal guardian. Older children (aged 15 years or above) will give written consent themselves.

Randomization

The participants will be allocated codes in a consecutive order; the code is randomly assigned to either the intervention phase (B) or control phase (A). Participating cancer units will be given the solution to the randomization code once the codes have been allocated to the participants.

Measures and materials

I) Impact evaluation

We consider a difference of 15% to be a meaningful difference in score average between T0 and T2 (48 hours); this is represented by a difference of approximately 1.5 units on the NRS (0-10) of distress, when comparing users of the PicPecc tool to control subjects. The estimate of standard deviation is based on unpublished data of 11 to 12-year-old girls' self-reports⁴⁰. Based on an expected standard deviation of 2.9 (and a power of 0.8), it is necessary to include at least 32 participants. With a dropout rate of approximately 20%, 20 participants in each group, i.e., 40 participants will be included in the study.

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3 In both the control (A) and intervention phases (B), the data collection follows the test-period
4 outline in Figure 2. Assessment of distress will be made at time-points T-1, T0, T1 and T2.
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7 T3 is an interview to evaluate the implementation process. Primary outcome is the difference
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9 in delta T0 and T2 between control and intervention phases (Fig. 2).
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15 *Insert figure 2*
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19 Primary outcome:
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21 The change in the primary outcome variable (distress) from baseline (T0) to 48 hours after
22 treatment start (T2) measured on an 11-point NRS (0 [no distress] and 10 [worst possible
23 distress])^{41 42} will be compared between the control and intervention phases. Self-reported
24 distress (NRS-11) will also be collected four hours before high-dose methotrexate (T-1), and
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32 after 24 hours (T1) (Fig. 2) in order to establish within subject variation.

33 Secondary outcomes:
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- 35 1. Blood samples will be collected and steroid levels in plasma will be monitored. Pain
36 and steroid levels in blood: neuropeptides, neurosteroids and peripheral steroids will
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60 be collected before start (T-1 and T0) of the high-dose methotrexate treatment, 24
hours after start (T1), and 48 hours after start (T2). Since blood-drawing procedures
are part of routine monitoring of cancer care, a small sample of the blood will be
obtained for this research, with no additional needle pricks required. Steroids are
measured in this study using LC-MS/MS and SFC-MS/MS methods⁴³.
2. Self-reported person-centredness. This is evaluated on the VCM⁴⁴, which will be
collected 48 hours after the start (T2) of the high-dose methotrexate treatment. The
VCM provides the legal guardians of children <7 years old (VCM 10Q-Legal
guardians), children aged 7-11 years (VCM 5Q) and adolescents aged 12 years and

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3 over (VCM 10Q) the opportunity to report their experiences regarding both the
4 meeting with the healthcare professional and their participation in decision related to
5 healthcare⁴⁴.
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11 3. Frequency of assessments of symptoms with the PicPecc tool. In-app assessment
12 levels will be recorded during the intervention phase, and during the control phase a
13 checklist will be used (e.g., frequency of symptom assessments T0-T2 (Fig 2)).
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15 4. Drug consumption for all types of symptom relief. These data will be collected from
16 the patients' medical records.
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24 II) Process evaluation

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26 After each intervention, experiences of care during the treatment are explored in individual
27 semi-structured interviews (T3) with all participating children, their legal guardians and the
28 healthcare professionals involved in the children's care. Numeric data regarding when and
29 how often the children used the PicPecc tool, will also be collected.
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35 The semi-structured interviews will follow an interview guide adapted for the child according
36 to age and maturity. The questions will also be provided with pictorial support according to
37 the concept of universal design (Supplementary file 1).
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45 *Intervention*

46 In the intervention phase the child will use the PicPecc tool before and during high-dose
47 methotrexate treatment for communicative support to assess their symptoms and emotions.
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50 The development of the PicPecc tool is presented elsewhere³⁴. The PicPecc tool is based on a
51 child-centred assessment approach, and the goal is to adapt the assessment to the child's age,
52 maturity, diagnosis, language ability, and cultural background. All sections of the PicPecc
53 tool will contain pictures, text, and sound. The PicPecc tool includes an assessment scale,
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3 which is designed as a thermometer. The thermometer is graded from zero (green) to ten
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5 (red). Each level of the scale is also symbolised with a face that shows the intensity of each
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7 symptom and/or emotion. The result of the assessment is visualized as a facial expression and
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9 colour that represents the intensity of the symptom and/or emotion (i.e., anxiety, appetite,
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11 fear, how I'm feeling today, nausea, pain, and sleep). In addition, the PicPecc tool has a body
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13 outline without any markings on which the child can indicate the location of the pain, pictures
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15 for the type of pain; as well as open questions where the child can write narratives about
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17 symptoms and/or emotions. The child receives visual feedback from the App and directly
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19 from healthcare professionals participating in the intervention, on their reported assessments
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21 made with the thermometer. The child can follow the assessments on an hourly, daily or
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23 weekly basis. The PicPecc tool also includes a personal avatar to represent the child. Using
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25 the avatar the child can make choices of the avatar's gender, skin and hair colour, and its
26
27 facial expressions thus contributing to the inclusiveness of the PicPecc tool by providing
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29 racial and gender diversity. The avatar will be linked to the child throughout all the
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31 assessments. In addition, in order to enhance interaction with the tool the design of the app
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33 includes a gamification element, e.g., the child will get a reward in the form of a pet when
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35 he/she has assessed the symptoms and/or emotions (Fig 3-5).
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Insert figure 3

Insert figure 4

Insert figure 5

The implementation of a person-centred approach in both phase A and phase B

The implementation strategies of person-centred communication consist of two components:

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3 (i) A person centred workshop for the paediatric oncology teams about enhanced
4 symptom communication;
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6
7 (ii) One member of the research team will be assigned to coach their colleagues in each
8 of the clinical departments on the person-centred approach. They will support the
9 implementation of the intervention and be responsible for data collection.
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17 i. Workshops with paediatric oncology teams

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19 Paediatric oncology teams will be invited to a workshop which will scrutinize and discuss
20 communication issues based on five questions. These questions will be 1) how
21 communication, based on a person-centred approach, can be implemented in clinical practice
22 in child healthcare? 2) Can universal design facilitate the implementation of person-centred
23 care for children? 3) What are the negative effects of distress for the child? 4) What are the
24 strategies to decrease distress, e.g., symptom management? 5) How can the PicPecc tool
25 enhance person-centred communication, and how it can be used in clinical practice? (Fig. 6).
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38 *Insert figure 6*

39 40 41 42 ii. Clinical coaches to support the implementation of the intervention

43
44 One coach in each of the clinical departments will support the implementation of the
45 intervention. The coach will be responsible for facilitating education and support for their
46 colleagues in the clinical department. In addition, the coaches will also be responsible for
47 data collection. The coach in each clinical ward will get support with the research process
48 from the research group.
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56 *Procedural fidelity*
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3 The procedural fidelity will be evaluated in each phase. The coach will (a) monitor the
4 occurrence of relevant variables, (b) provide documentation that the experimental conditions
5 occurred as planned, (c) provide support to practitioners about the use of the interventions.
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11 *Data analyses plan*

12 Effect evaluation

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15 We expect the intervention to be superior to the control in terms of the health outcome
16 assessment (NRS-11). We also expect that there will be a difference between pre
17 methotrexate treatment (T-1, T0) and methotrexate treatment (T1, T2) in both intervention
18 and control phases. Therefore, we will test the null hypothesis that there will be no change in
19 any of the measurements between the pre methotrexate treatment (T-1, T0) and methotrexate
20 treatment (T1, T2) nor between intervention and control phases. A p value of < 0.05 will be
21 considered as statistically significant. Categorical data will be descriptively analysed by
22 frequency distributions and percentages. The paired sample t-test will evaluate the difference
23 between two sets of assessments and effect size⁴⁵. Data will be analysed with IBM SPSS
24 Statistics 25 (New York City, USA).
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43 Process evaluation

44 The qualitative data analysis will be driven by interpretive description methodology, and the
45 analysis will follow a mixed-methods research design, i.e., a convergent design, with
46 concurrent timing where qualitative and quantitative data are independent of each other. The
47 goal is to disclose experiential and contextually shaped knowledge⁴⁶. The qualitative data
48 will be interpreted, and the analysis will lead to the identification of a set of themes which
49 describe the child's experience of using the tool. The quantitative data about the frequencies
50 of the participants' use of the PicPecc tool will be analysed with descriptive statistics, which
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3 will then be integrated with the qualitative analysis to facilitate a deeper understanding of
4
5 how the children use the PicPecc tool. Finally, an interpretation will be conducted between
6
7 qualitative and quantitative data⁴⁷.
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10 11 12 *Patient and public involvement*

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14 Children with cancer, legal guardians and their healthcare professionals have been involved
15
16 in the development of the PicPecc tool³⁴. Healthcare professionals have been involved in the
17
18 development of the hybrid design, in order to optimise the feasibility of the study.
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23 24 *Data monitoring committee*

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26 The study will have an external expert panel that will be responsible for checking the quality
27
28 of the data in the study. The expert panel will also evaluate ethical issues that emerge during
29
30 the study period.
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35 **Ethics and dissemination**

36 37 *Ethics*

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39 Ethical approval was obtained from the Swedish Ethical Review Authority (ref 2019-02392;
40
41 2020-02601) for the planned studies. Children are a vulnerable group since adults have a
42
43 power relationship with the child, the child with cancer is in a difficult life situation, and the
44
45 child is expected to share personal stories. All data collection is carried out during hospital
46
47 treatment, and all ordinary management and safety mechanisms are in place. If complications
48
49 occur in conjunction with the intervention, these are reported at the usual clinical rounds and
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51 will be managed according to the ordinary routines.
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3 The children and their parents will be informed about the purpose of the study. The
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5 information to participants states that all participation is voluntary and will not adversely
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7 affect the child's health-care, and that it is possible to withdraw consent without explanation
8
9 or any negative consequences on their treatment and care. All data will be kept confidential,
10
11 and it is only the research group that has access to the data. The results will not reveal the
12
13 identity of the participants. Research with children, legal guardians and healthcare
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15 professionals require oral and written consent and assent, and the research must not harm the
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17 individual.
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24 *Dissemination*

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26 Research findings will be presented at international cancer and paediatric conferences,
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28 published in scientific journals and publications for children with cancer and their legal
29
30 guardians. The results will also be available for professional training purposes.
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36
37 acquisition: S.N., A.W., J.B., J.C., E.J., K.K., T.L., A.S., M.S., G.T., A.H., J.Ö.
38
39 Methodology: S.N., J.B., J.C., M.S., J.Ö; Project administration: S.N.; Supervision: S.N.,
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41 J.B., J.C., M.S., J.Ö.; Visualisation: S.N.; Writing the original draft: S.N., A.W., J.B., J.C.,
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43 E.J., K.K., T.L., A.S., M.S., G.T., L.E., E.F., M.H., A.H., J.W., J.Ö.
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57

58 **Competing interests' statement:** The authors declare no conflict of interest.
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3 Fig. 1. The cross-over design with two study groups will participate in two phases as related
4 to the Nordic and European study protocols in Sweden for treatment of children with high-
5 dose methotrexate. All methotrexate treatment sessions take a similar amount of time for the
6 child. The intervals between each of the methotrexate treatments will be controlled by each
7 child's treatment plan and may vary between 3 and 6 weeks.
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17 Fig. 2. Data collection time-points and variables in both the control and intervention phases.
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21 Fig. 3. The PicPecc tool consists of an avatar and pets that the child can win through
22 interaction with the reporting process.
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28 Fig. 4. Reports are made by using a thermometer for assessing symptoms and emotions.
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33 Fig. 5. The child receives feedback on the assessments in the form of diagrams showing the
34 results of the latest days or weeks.
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40 Fig. 6. The questions for the workshops with communication and symptom management.
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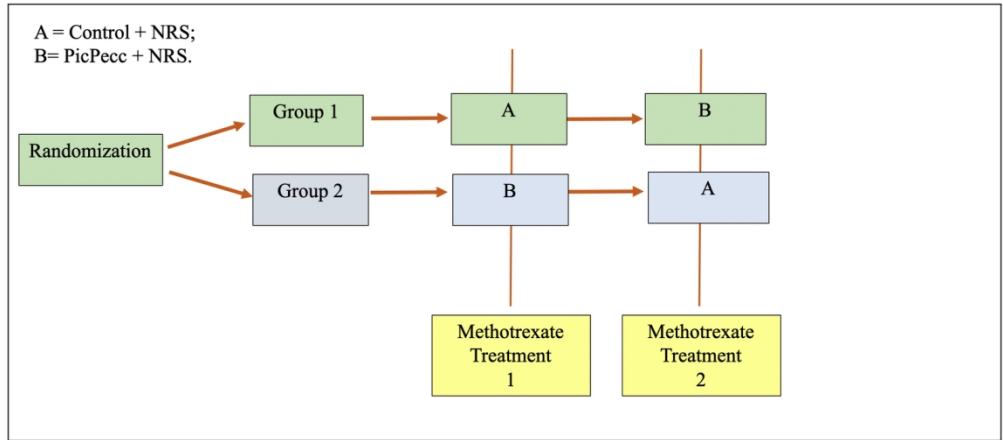


Fig. 1. The cross-over design with two study groups will participate in two phases as related to the Nordic and European study protocols in Sweden for treatment of children with high-dose methotrexate. All methotrexate treatment sessions take a similar amount of time for the child. The intervals between each of the methotrexate treatments will be controlled by each child's treatment plan and may vary between 3 and 6 weeks.

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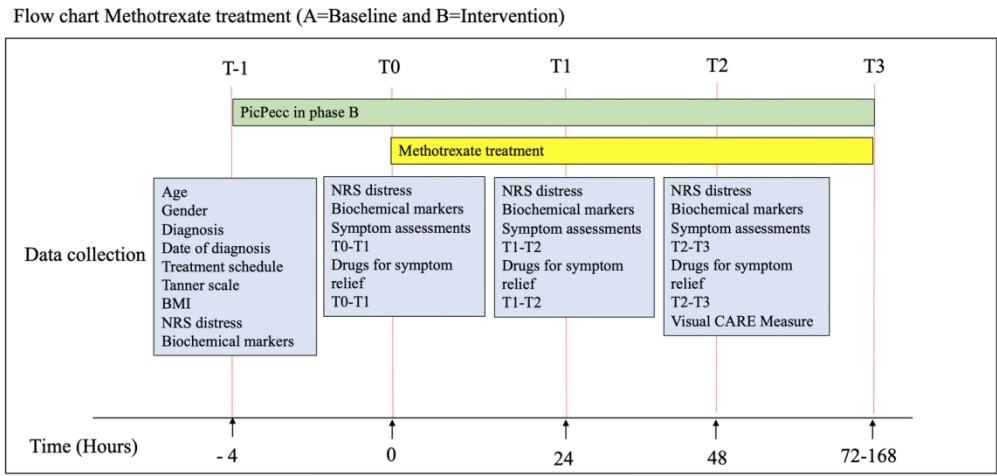


Fig. 2. Data collection time-points and variables in both the control and intervention phases.
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Fig. 3. The PicPecc tool consists of an avatar and pets that the child can win through interaction with the reporting process.

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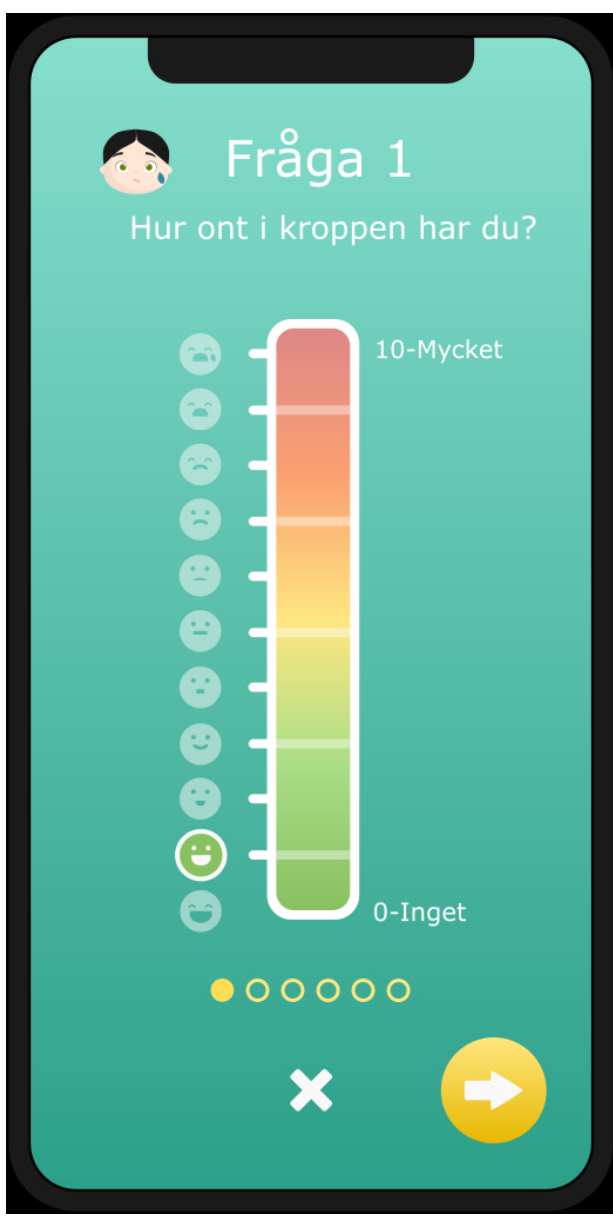


Fig. 4. Reports are made by using a thermometer for assessing symptoms and emotions.

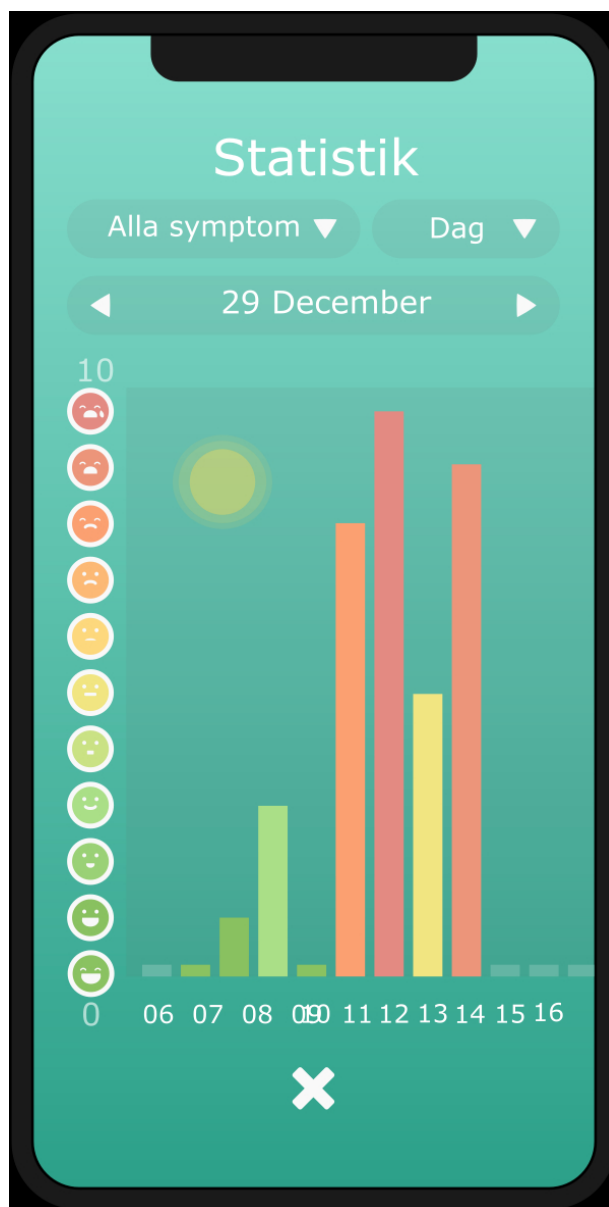


Fig. 5. The child receives feedback on the assessments in the form of diagrams showing the results of the latest days or weeks.

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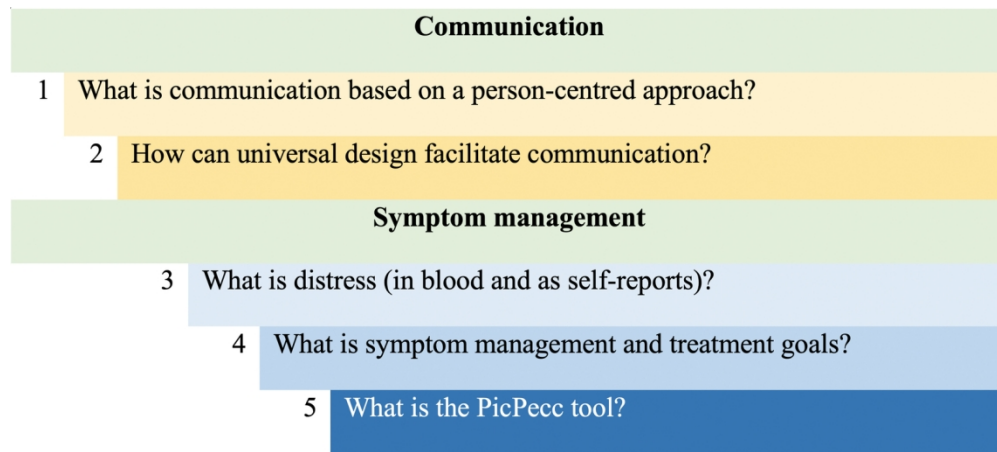


Fig. 6. The questions for the workshops with communication and symptom management.

141x63mm (300 x 300 DPI)

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3 Supplementary file 1. Interview questions in the process evaluation
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5 Main questions to the child:
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7 Tell me about your thoughts about getting your treatment.
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9 Did the healthcare professionals listen to your wishes?
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12 Tell me about a situation when you got support.
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14 Main questions to legal guardians:
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16 Tell me about your child's care.
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18 Did the healthcare professionals listen to you and your child's wishes?
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21 Tell me about a situation when your child got support.
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24 Main questions to healthcare professionals:
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26 Tell me about your experience of caring for the child.
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28 Do you think that the child felt listened to?
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31 Tell me about a situation when the child got support.
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Evaluating Pictorial support in Person-centred Care for Children (PicPecc): a protocol for a crossover design study.

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3 ***Title page***
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5 **Evaluating Pictorial support in Person-centred Care for Children (PicPecc): a protocol**
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7 **for a crossover design study.**
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Abstract

Introduction: This study protocol outlines the evaluation of the Pictorial support in Person-centred Care for Children (PicPecc). PicPecc is a digital tool used by children aged 5-17 years to self-report symptoms of acute lymphoblastic leukaemia, who undergo high-dose methotrexate treatments. The design of the digital platform follows the principles of universal design using pictorial support to provide accessibility for all children regardless of communication or language challenges and thus facilitating international comparison.

Methods and analysis: Both effect and process evaluations will be conducted. A crossover design will be used to measure the effect/outcome, and a mixed-methods design will be used to measure the process/implementation.

The primary outcome in the effect evaluation will be self-reported distress. Secondary outcomes will be: stress levels monitored via neuropeptides, neurosteroids and peripheral steroids indicated in plasma blood samples; frequency of in-app estimation of high levels of distress by the children; children's use of analgesic medicine; and person-centeredness evaluated via the questionnaire Visual CARE Measure.

For the process evaluation, qualitative interviews will be carried out with children with cancer, their legal guardians and case-related healthcare professionals. These interviews will address experiences with PicPecc in terms of feasibility and frequency of use from the child's perspective and value to the caseworker. Interview transcripts will be analysed using an interpretive description methodology.

Ethics and dissemination: Ethical approval was obtained from the Swedish Ethical Review Authority (ref 2019-02392; 2020-02601). Children, legal guardians, healthcare professionals, policymaking and research stakeholders will be involved in all stages of the research process according to Medical Research Council's guidelines. Research findings will be presented at international cancer and paediatric conferences and published in scientific journals.

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Trial registration: The trial is registered at ClinicalTrials.gov: NCT04433650

Keywords: Clinical trial; Paediatric oncology; Pain management; Qualitative research

For peer review only

Strengths and limitations of this study

- A person-centred framework is used for the design of the intervention.
- A child-centred pictorially supported communication device is used for self-report from the age of 5 years.
- The study evaluates a complex intervention with a combination of self-reported symptoms and biomarkers.
- Biomarkers of stress are monitored via blood plasma.
- The process evaluation will give additional information for future usage based on the frequency and feasibility of use.

Introduction

Children with cancer struggle with several physical and emotional symptoms. Their ability to communicate these symptoms is dependent on various factors, such as age, maturity, diagnosis, cognitive status, psychological status, language ability, and cultural background, as well as situational aspects. Alleviating distress caused by cancer is beneficial for both children, their families and healthcare professionals¹. Symptom identification and communicative support can enable symptom relief with the potential to reduce distress and alleviate suffering for the child, and will also improve quality of the care¹.

Person-centred care for children

Person-centred care is founded in ethics and based on the assumption that every person has resources that should be used in the care situation; being human is about having capabilities. This can be referred to Homo capax², i.e., a person with capabilities and vulnerabilities, and who is considered responsible for her/his actions in relationships with others³. There is no gold standard definition of person-centred care and the exploration of the concept has emphasized many different aspects and different definitions. In this project, the definition of person-centred paediatric care is based on three key concepts of partnership, narrative and documentation; generating a co-created partnership, and safeguarding the partnership through documenting the child's narrative, preferences and participation^{4 5}.

The project is founded on the ethical principles put forward by the French philosopher Paul Ricœur which aims for the good life, with and for others, with equitable and unbiased institutions⁶. In this regard a person-centred approach with a child perspective includes the idea of what is best for the child but also acknowledges the self-determination of the child. Decisions are therefore made that balance these concepts; that is, not solely from an adult's

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3 view of the child's needs nor solely from the perspective of the children themselves. Instead,
4 the desired solution is to combine the child's experience, the perspectives of legal guardians
5 and significant others and the healthcare professionals. Within this balance, however, it is
6 important to always prioritize the children's best interests in an attempt to optimize their
7 well-being⁷.

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17 To initiate a person-centred approach for paediatric care is to elucidate, listen to and affirm
18 the child's narrative. Assessments of symptoms are essential in symptom relief for children
19 with cancer, and self-reports are the gold standard for measuring symptoms^{8 9}.

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26 Children's own voices and self-reports are necessary to our understanding of the issues facing
27 children if we are to reach the goal of symptom relief⁷. Children with cancer – like all
28 children – have the right to actively take part in decisions regarding their health. In order to
29 achieve this, they need support to communicate issues related to their symptoms. For such a
30 system to work well in their everyday lives, symptom communication will largely rely on
31 identification of symptoms, and communication skills and pathways to present this
32 information in a timely and appropriate manner within their healthcare management¹⁰.

33 34 35 36 37 38 39 40 41 42 43 44 *Universal design*

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46 Healthcare professionals often tend to use language that is too complex for children to
47 understand. Children can therefore be said to be 'communication vulnerable'¹¹, depending on
48 their level of health literacy, potential cognitive or communicative disabilities, age, language
49 level or competency in the majority language¹². The Convention on the Rights of Persons
50 with Disabilities (CRPD) proposed the idea of 'universal design' to the design of products,
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3 environments, programmes and services so that they would be usable for all people, to the
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5 greatest extent possible, without the need for adaptation or specialised knowledge¹³.
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10 The application of new digital technologies using pictorial supported communication may
11 assist communication vulnerable children in healthcare to more effectively self-report and
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13 communicate with others about their symptoms, overcoming their, and possibly their
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15 families' communication difficulties. Pictorial communication support may foster closer
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17 relationships, trust and more open communication between families and healthcare
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19 professionals¹⁴.
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26 *Self-assessment tools*

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28 The development of assessment tools for children to self-report pain started in the 1980s,
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30 with the widespread implementation of these tools in the 1990s¹⁵. However, children's self-
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32 reports have been shown to still fail to impact healthcare, and there is a need for innovative
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34 ideas that support the implementation of these assessment tools in clinical practice^{16 17}.
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37 Enabling children with cancer to self-report their symptoms may help them to understand
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39 their condition better and thereby better cope with their illness. Communicating symptoms in
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41 an effective way that can quickly alert healthcare professionals to their discomfort is an
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43 empowering process that will make them feel secure in knowing that they have strategies that
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45 give them the possibility to communicate with somebody who will assist them to achieve
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47 symptom relief¹⁸.
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53 Although validated patient self-report instruments exist for some symptoms healthcare
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55 professionals seldom use these in clinical practice¹⁷ furthermore most paediatric conditions
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57 lack a validated symptom assessment tool. What is missing from the clinical toolbox is an
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3 instrument that assesses the intensity of symptoms in a simple, valid and reliable way¹⁹. One
4 of few symptoms that is assessed in clinical practice is pain intensity. Smeland et al. (2018)
5 found that, overall, pain was assessed using a validated tool in 19% of the children in post
6 anaesthesia care; this fell to 9% in children aged <5 years old¹⁷. An explanation for this could
7 be either that these instruments do not exist or that they are difficult to use, interpret or
8 unreliable. Healthcare professionals prefer to rely on personal judgement and experience
9 with the patient and family²⁰ and therefore the measurement process must contribute to this
10 and not try to replace it. The use of an instrument that focuses on a single symptom, for
11 example pain intensity, does not adequately capture the overall experience of the child and
12 can be considered a restrictive application. Novel assessment tools that give a broader
13 description of symptoms are therefore needed in order that the child can fully communicate
14 their experience.

33 *Distress in children*

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35 The term "distress" refers to a multifactorial unpleasant emotional experience that can be
36 described as a combination of fear, anxiety, and pain²¹. The relationships between these
37 factors are complex, and the experience of distress is based on interactions between
38 "genetically linked behaviour patterns, temperamental predispositions, normal developmental
39 fears, parental psychopathology, and discrete learning experiences"²². Distress in this study is
40 defined as an experiential response and sensation of the mind associated with negative
41 emotions that appear when a situation is fearful or impossible to manage from the perspective
42 of the child. Distress can be a consequence of insufficient symptom relief, and self-reported
43 distress is a global assessment that reflects the child's experience of the success of symptom
44 relief. It is important to evaluate the distress in children undergoing cancer treatment and to
45 find strategies for the measurements of symptoms/emotions that are reliable and valid for this
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3 purpose. It is known that acute stress activates the hypothalamic–pituitary–adrenal (HPA)
4 axis and the sympathetic nervous system (SNS), as well as the hypothalamic–pituitary–
5 gonadal (HPG) axis²³⁻²⁵. For example, plasma cortisol concentration is an established stress
6 (energy mobilization) indicator that is known to react within minutes after the onset of stress
7 exposure. Estradiol is on the other hand an anabolic hormone, which protects against adverse
8 effects of stress.
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19 *The medical scenario within which PicPecc will be tested*

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21 The drugs used to treat children with cancer can lead to several negative side-effects, e.g.,
22 children undergoing cancer treatment frequently report nausea and vomiting and other kind of
23 distress²⁶. One of the drugs that is used in cancer treatment is methotrexate which is one of
24 the most effective medications in the treatment of acute lymphoblastic leukaemia (ALL) in
25 children²⁷. High-dose methotrexate is used world-wide and has been included as part of the
26 Nordic Society for Paediatric Haematology and Oncology acute lymphoblastic leukaemia
27 treatment protocols since 1981²⁸. Furthermore, the treatment is given according to a strictly
28 detailed Nordic and European schedules, i.e., clinical conditions have been well established.
29 For these reasons, treatment with high-dose methotrexate has been chosen as the medical
30 context within which the effect of the use of PicPecc tool will be evaluated from a person-
31 centred perspective.
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49 The primary aim of the project is to investigate whether a person-centred communication
50 intervention through the use of the PicPecc digital communication tool for children
51 undergoing cancer treatment decrease the children's symptom-related distress in general. A
52 secondary aim is to investigate the process of implementing person-centred communication
53 through the use of the PicPecc tool.
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3 *Main research question:*
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5 Does adding the PicPecc tool decrease distress (measured on an 11-point numeric rating scale
6 (NRS) (0 [no distress] and 10 [worst possible distress]) in children with ALL, aged 5-17
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8 years, who undergo high-dose methotrexate treatment?
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15 *Secondary research questions:*
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- 17 (i) Does the application of the PicPecc tool, increase person-centredness (measured
18 on VCM (Visual CARE Measure) in children with ALL, aged 5-17 years, who
19 undergo high-dose methotrexate treatment?
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26 (ii) Does the application of the PicPecc tool, alter stakeholders' perspectives on
27 person-centred communication?
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33 *Hypothesis*
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- 35 (i) Children undergoing cancer treatment will experience lower distress levels, when
36 they can report their holistic symptoms in a system created using universal design
37 principles (i.e. the PicPecc tool with pictorial support) than will children with
38 standard healthcare communication opportunities (the primary outcome). In
39 addition to a decrease in self-reported stress levels there will also be a decrease in
40 neuropeptides, neurosteroids and peripheral steroids for stress and pain.
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51 (ii) Person-centred care is enhanced, through enabling children to proactively assess
52 their symptoms from a holistic perspective and communicate these to their
53 healthcare providers within an enhanced communication framework (i.e. using the
54 PicPecc tool).
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Methods and analysis

Study design

The Medical Research Council's key principles and actions for development and evaluation of complex interventions^{29 30} guided the intervention development and the research design. In a hybrid design, both the effects of the intervention and the implementation process will be evaluated³¹. Relevant care situations are selected³² where highly standardized care procedures are used and where there are a range of different situations where children struggle with symptoms. To facilitate the effect evaluation, the children will participate in a crossover design study where they are their own controls (Fig 1). The study design follows the SPENT 2019 checklist for clinical trials³³.

The development of the PicPecc tool follows established guidelines³⁴ and was based on the theoretical framework of person-centred care⁴, on published systematic reviews⁹ and on systematic reviews conducted within the project on assessment tools for nausea³⁵, and anxiety³⁶. Children with cancer, their legal guardians and healthcare professionals have been involved throughout the development process. The study protocol outlined here pertains to the evaluation and implementation phases.

Insert figure 1

Participants and units

Context and setting

In Sweden, approximately 350 children are diagnosed with cancer each year. The treatment of childhood cancer is conducted at six childhood cancer centres and at regional hospitals³⁷.

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3 Three of these childhood cancer centres and five regional hospitals in Sweden will participate
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5 in the study.
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10 Selection criteria

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12 Inclusion criteria are children diagnosed with ALL, between 5 and 17 years of age whose
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14 treatment-plan includes at least two treatments of high-dose methotrexate, including children
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16 with relapsed disease. The child needs to have a cognitive level of at least five years (i.e., to
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18 be able to understand an NRS³⁸). The child's understanding of an NRS will be tested before
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20 inclusion based on a situational judgment test which involves a realistic, hypothetical
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22 scenario about a child who fell from a tree. The child will be asked to assess pain using the
23
24 NRS. This situational judgment test has previously been validated to discriminate positive
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26 and negative emotions³⁹. Exclusion criteria are children 0-4 years, non-completion of consent
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28 forms, scheduled to undergo only one high-dose methotrexate treatment.
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35 The children's legal guardians and the healthcare providers who take care of these children
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37 will be included in the assessment, in addition to the children themselves.
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42 Method of recruitment

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44 The recruitment is planned to start in the beginning of 2021. The surveyed children
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46 participate in data collection twice, once as a control (A) and once at the time of symptom
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48 reporting and initial use of the communication tool PicPecc (B) (Fig. 1). Children with cancer
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50 aged 5-17 years old, legal guardians and healthcare professionals at three childhood cancer
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52 centres and five regional hospitals in Southern Sweden will participate in the study. Each
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54 year approximately 175-200 children get cancer in Southern Sweden, and about a third of
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56 these children receive a diagnosis of ALL.
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Consent process

Legal guardians of children below 15 years of age with ALL who are scheduled to receive high-dose methotrexate treatments will be informed about the study by a physician or a nurse, included in the research group. The legal guardian will receive written information, and the child will be given text and picture-based information. Child assent is obtained verbally upon consent from a legal guardian. Older children (aged 15 years or above) will give written consent themselves. In Sweden, children over 15 years must provide written informed consent in addition to that provided by their legal guardians if they have the capacity to understand the consequences of participation.

Randomization

The participants will be allocated codes in a consecutive order; the code is randomly assigned to either the intervention phase (B) or control phase (A). Participating cancer units will be given the solution to the randomization code once the codes have been allocated to the participants. The participants will only have access to the PicPecc tool during the intervention phase. There will be a period of at least two weeks between the end of the first intervention period and the start of the next methotrexate treatment. This provides an adequate washout period between the intervention (B) and the control phase (A) for any behaviour change to revert to previous patterns. Following the transtheoretical model⁴⁰ habitual behaviour change related to health is a process involving a number of stages which takes time to complete successfully. Where support for change is removed early in the process the individual will quickly revert to previous habituated behavioural patterns. We are confident therefore, that the intervention will have no residual effects on the control phase.

Measures and materials

I) Impact evaluation

We consider a difference of 15% to be a meaningful difference in score average between T0 and T2 (48 hours); this is represented by a difference of approximately 1.5 units on the NRS (0-10) of distress, when comparing users of the PicPecc tool to control subjects. The estimate of standard deviation is based on unpublished data of 11 to 12-year-old girls' self-reports⁴¹. Based on an expected standard deviation of 2.9 (and a power of 0.8), it is necessary to include at least 32 participants. With a dropout rate of approximately 20%, 20 participants in each group, i.e., 40 participants will be included in the study.

In both the control (A) and intervention phases (B), the data collection follows the test-period outline in Figure 2. Assessment of distress will be made at time points T-1, T0, T1 and T2. T3 is an interview to evaluate the implementation process. Primary outcome is the difference in delta T0 and T2 between control and intervention phases. The time points are linked to the schedule for the methotrexate treatment to avoid extra blood sampling. The time points will also facilitate the evaluation between before and after treatment, with the objective to evaluate differences in symptoms, with and without the PicPecc tool (Fig. 2).

Insert figure 2

Primary outcome:

The change in the primary outcome variable (distress) from baseline (T0) to 48 hours after treatment start (T2) measured on an 11-point NRS (0 [no distress] and 10 [worst possible distress])^{42 43} will be compared between the control and intervention phases. Self-reported

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3 distress (NRS-11) will also be collected four hours before high-dose methotrexate (T-1), and
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5 after 24 hours (T1) (Fig. 2) in order to establish within subject variation.
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8 Secondary outcomes:
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- 10 1. Blood samples will be collected and steroid levels in plasma will be monitored. Pain
11 and steroid levels in blood: neuropeptides, neurosteroids and peripheral steroids will
12 be collected before start (T-1 and T0) of the high-dose methotrexate treatment, 24
13 hours after start (T1), and 48 hours after start (T2). Since blood-drawing procedures
14 are part of routine monitoring of cancer care, a small sample of the blood will be
15 obtained for this research, with no additional needle pricks required. Steroids are
16 measured in this study using LC-MS/MS and SFC-MS/MS methods⁴⁴. It is not
17 possible to distinguish between different types of stress, but the design includes the
18 evaluation of two indicators of stress response, firstly, biological (measured by
19 biomarkers) and secondly, perceived (self-reported). Since the same individual is
20 assessed before and after the chemotherapy, both with and without the PicPecc tool, it
21 is possible to evaluate the effect of the PicPecc tool on intervention-related stress.
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37 2. Self-reported person-centredness. This is evaluated on the VCM⁴⁵, which will be
38 collected 48 hours after the start (T2) of the high-dose methotrexate treatment. The
39 VCM provides the legal guardians of children <7 years old (VCM 10Q-Legal
40 guardians), children aged 7-11 years (VCM 5Q) and adolescents aged 12 years and
41 over (VCM 10Q) the opportunity to report their experiences regarding both the
42 meeting with the healthcare professional and their participation in decision related to
43 healthcare⁴⁴.
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54 3. Frequency of assessments of symptoms with the PicPecc tool. In-app assessment
55 levels will be recorded during the intervention phase, and during the control phase a
56 checklist will be used (e.g., frequency of symptom assessments T0-T2 (Fig 2)).
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3 4. Drug consumption for all types of symptom relief. These data will be collected from
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5 the patients' medical records.
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10 II) Process evaluation

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12 After each intervention, experiences of care during the treatment are explored in individual
13 semi-structured interviews (T3) with all participating children, their legal guardians and the
14 healthcare professionals involved in the children's care. The objective is to illuminate the
15 experiences of using the PicPecc tool from the perspective of the participating children, their
16 legal guardians and the healthcare professionals. The interviews will be thematically analysed
17 following the procedures of Braun and Clarke⁴⁶ to give an understanding of how the PicPecc
18 tool was used during the intervention.
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30 Numeric data regarding when and how often the children used the PicPecc tool, will also be
31 collected.
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34 The semi-structured interviews will follow an interview guide adapted for the child according
35 to age and maturity. The questions will also be provided with pictorial support according to
36 the concept of universal design (Supplementary file 1).
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45 *Intervention*

46 In the intervention phase the child will use the PicPecc tool before and during high-dose
47 methotrexate treatment for communicative support to assess their symptoms and emotions.
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49 The PicPecc tool is used in a phone or a tablet computer; delivered via an iOS or Android
50 platform. The development of the PicPecc tool is presented elsewhere³⁴. The PicPecc tool is
51 based on a child-centred assessment approach, and the goal is to adapt the assessment to the
52 child's age, maturity, diagnosis, language ability, and cultural background. All sections of the
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3 PicPecc tool will contain pictures, text, and sound. The PicPecc tool includes an assessment
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5 scale, which is designed as a thermometer. The thermometer is graded from zero (green) to
6
7 ten (red). Each level of the scale is also symbolised with a face that shows the intensity of
8
9 each symptom and/or emotion. The result of the assessment is visualized as a facial
10
11 expression and colour that represents the intensity of the symptom and/or emotion (i.e.,
12
13 anxiety, appetite, fear, how I'm feeling today, nausea, pain, and sleep). In addition, the
14
15 PicPecc tool has a body outline without any markings on which the child can indicate the
16
17 location of the symptom and/or emotion, pictures for the type of symptom and/or emotion; as
18
19 well as open questions where the child can write narratives about symptoms and/or emotions.
20
21 The child receives visual feedback from the app and directly from healthcare professionals
22
23 participating in the intervention, on their reported assessments made with the thermometer.
24
25 The child can follow the assessments on an hourly, daily or weekly basis. The PicPecc tool
26
27 also includes a personal avatar to represent the child. Using the avatar the child can make
28
29 choices of the avatar's gender, skin and hair colour, and its facial expressions thus
30
31 contributing to the inclusiveness of the PicPecc tool by providing racial and gender diversity.
32
33 The avatar will be linked to the child throughout all the assessments. In addition, in order to
34
35 enhance interaction with the tool the design of the app includes a gamification element, e.g.,
36
37 the child will get a reward in the form of a pet when he/she has assessed the symptoms and/or
38
39 emotions (Fig 3-5). The child is encouraged with a reminder in the PicPecc tool to assess the
40
41 symptoms and/or emotions twice daily (in the morning and in the evening). The child can in
42
43 addition assess his/her symptoms and/or emotions more frequently with the PicPecc tool, e.g.,
44
45 if he or she prefers to do so.
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56 *Insert figure 3*
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3 *Insert figure 4*
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8 *Insert figure 5*
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11
12 *The implementation of a person-centred approach in both phase A and phase B*
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14
15 The implementation strategies of person-centred communication consist of two components:

- 16
17 (i) A person centred workshop for the paediatric oncology teams about enhanced
18 symptom communication;
19
20
21 (ii) One member of the research team will be assigned to coach their colleagues in each
22 of the clinical departments on the person-centred approach. They will support the
23 implementation of the intervention and be responsible for data collection.
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30
31 i. Workshops with paediatric oncology teams
32

33 Paediatric oncology teams will be invited to a workshop which will scrutinize and discuss
34 communication issues based on five questions. These questions will be 1) how
35 communication, based on a person-centred approach, can be implemented in clinical practice
36
37 in child healthcare? 2) Can universal design facilitate the implementation of person-centred
38 care for children? 3) What are the negative effects of distress for the child? 4) What are the
39 strategies to decrease distress, e.g., symptom management? 5) How can the PicPecc tool
40 enhance person-centred communication, and how it can be used in clinical practice? (Fig. 6).
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51 *Insert figure 6*
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56 ii. Clinical coaches to support the implementation of the intervention
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3 One coach in each of the clinical departments will support the implementation of the
4
5 intervention. The coach will be responsible for facilitating education and support for their
6
7 colleagues in the clinical department. In addition, the coaches will also be responsible for
8
9 data collection. The coach in each clinical ward will get support with the research process
10
11 from the research group.
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17 *Procedural fidelity*

18
19 The procedural fidelity will be evaluated in each phase. The coach will (a) monitor the
20
21 occurrence of relevant variables, (b) provide documentation that the experimental conditions
22
23 occurred as planned, (c) provide support to practitioners about the use of the interventions.
24
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28 *Data analyses plan*

29 Effect evaluation

30
31 We expect the intervention to be superior to the control in terms of the health outcome
32
33 assessment (NRS-11). We also expect that there will be a difference between pre
34
35 methotrexate treatment (T-1, T0) and methotrexate treatment (T1, T2) in both intervention
36
37 and control phases. Therefore, we will test the null hypothesis that there will be no change in
38
39 any of the measurements between the pre methotrexate treatment (T-1, T0) and methotrexate
40
41 treatment (T1, T2) nor between intervention and control phases. A p value of < 0.05 will be
42
43 considered as statistically significant. Categorical data will be descriptively analysed by
44
45 frequency distributions and percentages. The paired sample t-test will evaluate the difference
46
47 between two sets of assessments and effect size⁴⁷. Data will be analysed with IBM SPSS
48
49 Statistics 25 (New York City, USA).
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58 Process evaluation

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3 The qualitative data analysis will be driven by interpretive description methodology, and the
4 analysis will follow a mixed-methods research design, i.e., a convergent design, with
5 concurrent timing where qualitative and quantitative data are independent of each other. The
6 goal is to disclose experiential and contextually shaped knowledge⁴⁸. The qualitative data
7 will be interpreted, and the analysis will lead to the identification of a set of themes which
8 describe the child's experience of using the tool. The quantitative data about the frequencies
9 of the participants' use of the PicPecc tool will be analysed with descriptive statistics, which
10 will then be integrated with the qualitative analysis to facilitate a deeper understanding of
11 how the children use the PicPecc tool. Finally, an interpretation will be conducted between
12 qualitative and quantitative data⁴⁹.
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28 *Patient and public involvement*

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30 Children with cancer, legal guardians and their healthcare professionals have been involved
31 in the development of the PicPecc tool³⁴. Healthcare professionals have been involved in the
32 development of the hybrid design, in order to optimise the feasibility of the study.
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40 *Data monitoring committee*

41
42 The study will have an external expert panel that will be responsible for checking the quality
43 of the data in the study. The expert panel will also evaluate ethical issues that emerge during
44 the study period.
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51 **Ethics and dissemination**

52 *Ethics*

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54 Ethical approval was obtained from the Swedish Ethical Review Authority (ref 2019-02392;
55 2020-02601) for the planned studies. Children are a vulnerable group since adults have a
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3 power relationship with the child, the child with cancer is in a difficult life situation, and the
4
5 child is expected to share personal stories. All data collection is carried out during hospital
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7 treatment, and all ordinary management and safety mechanisms are in place. If complications
8
9 occur in conjunction with the intervention, these are reported at the usual clinical rounds and
10
11 will be managed according to the ordinary routines.
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17 The children and their legal guardians will be informed about the purpose of the study. The
18
19 information to participants states that all participation is voluntary and will not adversely
20
21 affect the child's health-care, and that it is possible to withdraw consent without explanation
22
23 or any negative consequences on their treatment and care. All data will be kept confidential,
24
25 and it is only the research group that has access to the data. The results will not reveal the
26
27 identity of the participants. Research with children, legal guardians and healthcare
28
29 professionals require oral and written consent and assent, and the research must not harm the
30
31 individual.
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35
36

37 *Dissemination*

38
39 Research findings will be presented at international cancer and paediatric conferences,
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41 published in scientific journals and publications for children with cancer and their legal
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43 guardians. The results will also be available for professional training purposes.
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16 acquisition: S.N., A.W., J.B., J.C., E.J., K.K., T.L., A.S., M.S., G.T., A.H., J.Ö.
17
18 Methodology: S.N., J.B., J.C., M.S., J.Ö; Project administration: S.N.; Supervision: S.N.,
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20 J.B., J.C, M.S., J.Ö.; Visualisation: S.N.; Writing the original draft: S.N., A.W., J.B., J.C.,
21
22 E.J., K.K., T.L., A.S., M.S., G.T., L.E., E.F., M.H., A.H., J.W., J.Ö.
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40 **Competing interests' statement:** The authors declare no conflict of interest.
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45 **Figure Legends**

46
47 Fig. 1. The cross-over design with two study groups will participate in two phases as related
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49 to the Nordic and European study protocols in Sweden for treatment of children with high-
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51 dose methotrexate. All methotrexate treatment sessions take a similar amount of time for the
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53 child. The intervals between each of the methotrexate treatments will be controlled by each
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55 child's treatment plan and may vary between 3 and 6 weeks.
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3 Fig. 2. Data collection time points and variables in both the control and intervention phases.
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8 Fig. 3. The PicPecc tool consists of an avatar and pets that the child can win through
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10 interaction with the reporting process.
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15 Fig. 4. Reports are made by using a thermometer for assessing symptoms and emotions.
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20 Fig. 5. The child receives feedback on the assessments in the form of diagrams showing the
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22 results of the latest days or weeks.
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27 Fig. 6. The questions for the workshops with communication and symptom management.
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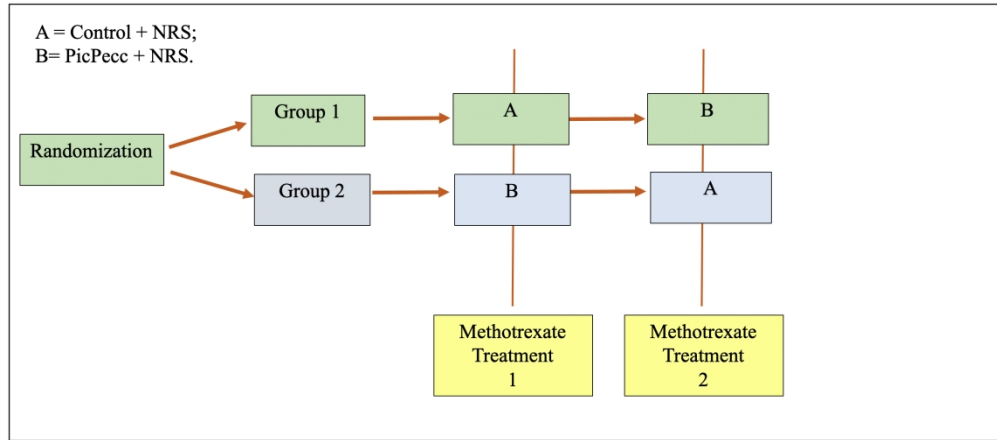


Fig. 1. The cross-over design with two study groups will participate in two phases as related to the Nordic and European study protocols in Sweden for treatment of children with high-dose methotrexate. All methotrexate treatment sessions take a similar amount of time for the child. The intervals between each of the methotrexate treatments will be controlled by each child's treatment plan and may vary between 3 and 6 weeks.

136x60mm (500 x 500 DPI)

Flow chart Methotrexate treatment (A=Baseline and B=Intervention)

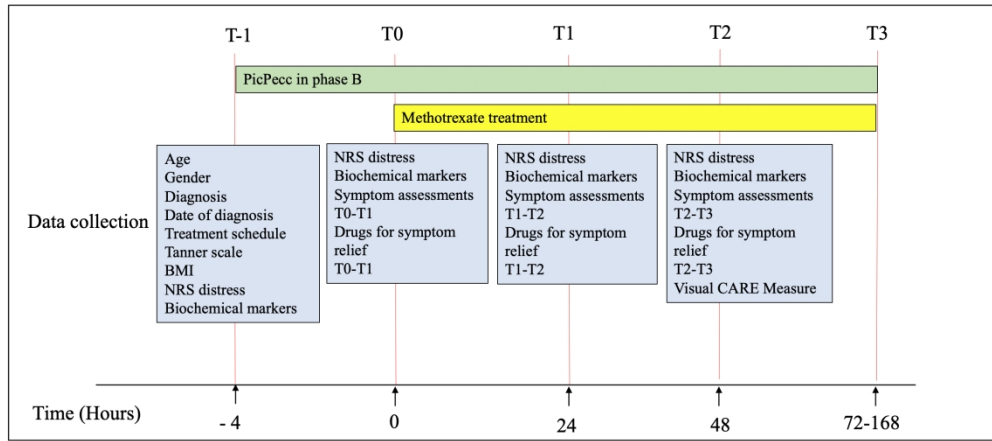


Fig. 2. Data collection time-points and variables in both the control and intervention phases.

137x65mm (500 x 500 DPI)



Figure 3. The PicPecc tool consists of an avatar and pets that the child can win through interaction with the reporting process.

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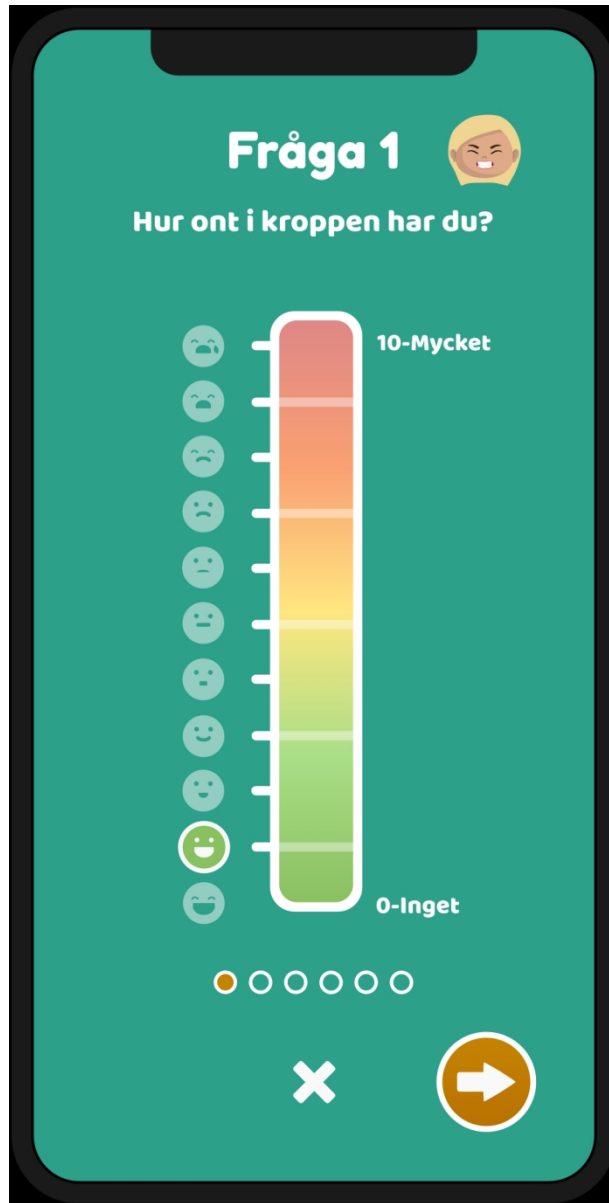


Figure 4. Reports are made by using a thermometer for assessing symptoms and emotions.

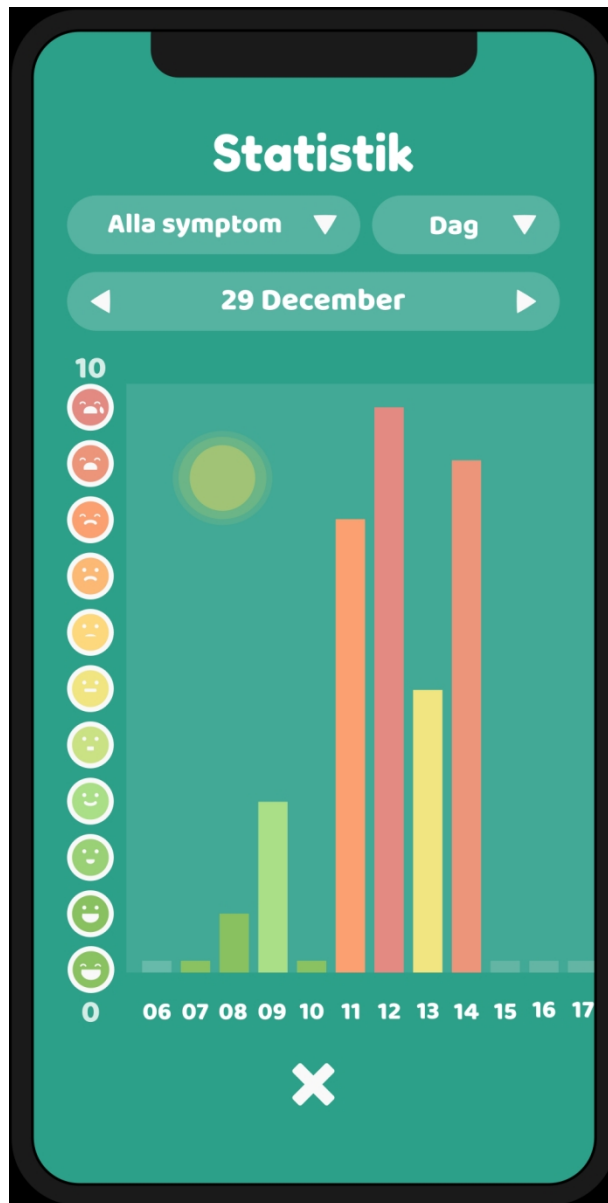


Figure 5. The child receives feedback on the assessments in the form of diagrams showing the results of the latest days or weeks.

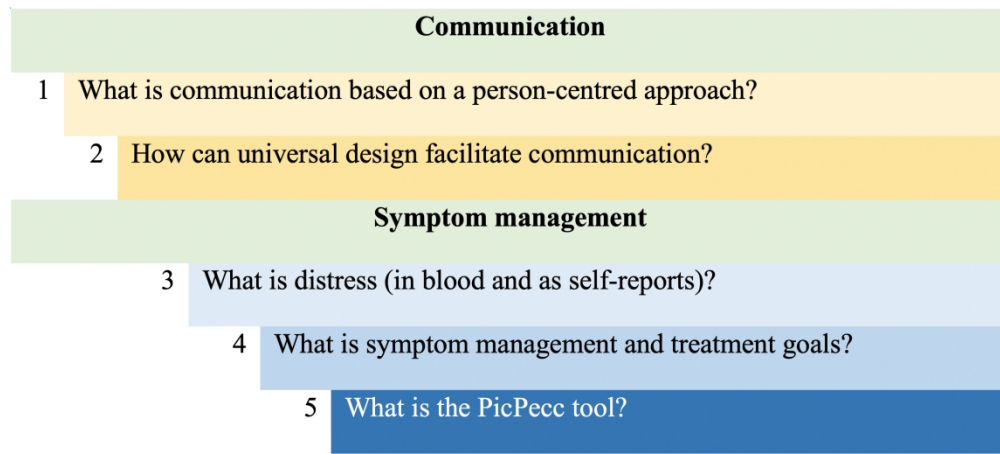


Fig. 6. The questions for the workshops with communication and symptom management.

141x63mm (500 x 500 DPI)

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3 Supplementary file 1. Interview questions in the process evaluation
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5 Main questions to the child:
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7 Tell me about your thoughts about getting your treatment.
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9 Did the healthcare professionals listen to your wishes?
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12 Tell me about a situation when you got support.
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14 Main questions to legal guardians:
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16 Tell me about your child's care.
17

18 Did the healthcare professionals listen to you and your child's wishes?
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21 Tell me about a situation when your child got support.
22
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24 Main questions to healthcare professionals:
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26 Tell me about your experience of caring for the child.
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28 Do you think that the child felt listened to?
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31 Tell me about a situation when the child got support.
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BMJ Open

Evaluating Pictorial support in Person-centred Care for Children (PicPecc): a protocol for a crossover design study.

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2
3 ***Title page***
4

5 **Evaluating Pictorial support in Person-centred Care for Children (PicPecc): a protocol**
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7 **for a crossover design study.**
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Abstract

Introduction: This study protocol outlines the evaluation of the Pictorial support in Person-centred Care for Children (PicPecc). PicPecc is a digital tool used by children aged 5-17 years to self-report symptoms of acute lymphoblastic leukaemia, who undergo high-dose methotrexate treatments. The design of the digital platform follows the principles of universal design using pictorial support to provide accessibility for all children regardless of communication or language challenges and thus facilitating international comparison.

Methods and analysis: Both effect and process evaluations will be conducted. A crossover design will be used to measure the effect/outcome, and a mixed-methods design will be used to measure the process/implementation.

The primary outcome in the effect evaluation will be self-reported distress. Secondary outcomes will be: stress levels monitored via neuropeptides, neurosteroids and peripheral steroids indicated in plasma blood samples; frequency of in-app estimation of high levels of distress by the children; children's use of analgesic medicine; and person-centeredness evaluated via the questionnaire Visual CARE Measure.

For the process evaluation, qualitative interviews will be carried out with children with cancer, their legal guardians and case-related healthcare professionals. These interviews will address experiences with PicPecc in terms of feasibility and frequency of use from the child's perspective and value to the caseworker. Interview transcripts will be analysed using an interpretive description methodology.

Ethics and dissemination: Ethical approval was obtained from the Swedish Ethical Review Authority (ref 2019-02392; 2020-02601; 2020-06226). Children, legal guardians, healthcare professionals, policymaking and research stakeholders will be involved in all stages of the research process according to Medical Research Council's guidelines. Research findings will

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3 be presented at international cancer and paediatric conferences and published in scientific
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5 journals.
6

7 *Trial registration:* The trial is registered at ClinicalTrials.gov: NCT04433650
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12 **Keywords:** Clinical trial; Paediatric oncology; Pain management; Qualitative research
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For peer review only

Strengths and limitations of this study

- A person-centred framework is used for the design of the intervention.
- A child-centred pictorially supported communication device is used for self-report from the age of 5 years.
- The study evaluates a complex intervention with a combination of self-reported symptoms and biomarkers.
- Biomarkers of stress are monitored via blood plasma.
- The process evaluation will give additional information for future usage based on the frequency and feasibility of use.

Introduction

Children with cancer struggle with several physical and emotional symptoms. Their ability to communicate these symptoms is dependent on various factors, such as age, maturity, diagnosis, cognitive status, psychological status, language ability, and cultural background, as well as situational aspects. Alleviating distress caused by cancer is beneficial for both children, their families and healthcare professionals¹. Symptom identification and communicative support can enable symptom relief with the potential to reduce distress and alleviate suffering for the child, and will also improve quality of the care¹.

Person-centred care for children

Person-centred care is founded in ethics and based on the assumption that every person has resources that should be used in the care situation; being human is about having capabilities. This can be referred to Homo capax², i.e., a person with capabilities and vulnerabilities, and who is considered responsible for her/his actions in relationships with others³. There is no gold standard definition of person-centred care and the exploration of the concept has emphasized many different aspects and different definitions. In this project, the definition of person-centred paediatric care is based on three key concepts of partnership, narrative and documentation; generating a co-created partnership, and safeguarding the partnership through documenting the child's narrative, preferences and participation^{4 5}.

The project is founded on the ethical principles put forward by the French philosopher Paul Ricœur which aims for the good life, with and for others, with equitable and unbiased institutions⁶. In this regard a person-centred approach with a child perspective includes the idea of what is best for the child but also acknowledges the self-determination of the child. Decisions are therefore made that balance these concepts; that is, not solely from an adult's

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3 view of the child's needs nor solely from the perspective of the children themselves. Instead,
4 the desired solution is to combine the child's experience, the perspectives of legal guardians
5 and significant others and the healthcare professionals. Within this balance, however, it is
6 important to always prioritize the children's best interests in an attempt to optimize their
7 well-being⁷.

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17 To initiate a person-centred approach for paediatric care is to elucidate, listen to and affirm
18 the child's narrative. Assessments of symptoms are essential in symptom relief for children
19 with cancer, and self-reports are the gold standard for measuring symptoms^{8 9}.

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26 Children's own voices and self-reports are necessary to our understanding of the issues facing
27 children if we are to reach the goal of symptom relief⁷. Children with cancer – like all
28 children – have the right to actively take part in decisions regarding their health. In order to
29 achieve this, they need support to communicate issues related to their symptoms. For such a
30 system to work well in their everyday lives, symptom communication will largely rely on
31 identification of symptoms, and communication skills and pathways to present this
32 information in a timely and appropriate manner within their healthcare management¹⁰.

33 34 35 36 37 38 39 40 41 42 43 44 *Universal design*

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46 Healthcare professionals often tend to use language that is too complex for children to
47 understand. Children can therefore be said to be 'communication vulnerable'¹¹, depending on
48 their level of health literacy, potential cognitive or communicative disabilities, age, language
49 level or competency in the majority language¹². The Convention on the Rights of Persons
50 with Disabilities (CRPD) put forth the idea of 'universal design' to the design of products,
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3 environments, programmes and services so that they would be usable for all people, to the
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5 greatest extent possible, without the need for adaptation or specialised knowledge¹³.
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10 The application of new digital technologies using pictorial supported communication may
11 assist communication vulnerable children in healthcare to more effectively self-report and
12
13 communicate with others about their symptoms, overcoming their, and possibly their
14
15 families' communication difficulties. Pictorial communication support may foster closer
16
17 relationships, trust and more open communication between families and healthcare
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19 professionals¹⁴.
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26 *Self-assessment tools*

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28 The development of assessment tools for children to self-report pain started in the 1980s,
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30 with the widespread implementation of these tools in the 1990s¹⁵. However, children's self-
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32 reports have been shown to still fail to impact healthcare, and there is a need for innovative
33
34 ideas that support the implementation of these assessment tools in clinical practice^{16 17}.
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37 Enabling children with cancer to self-report their symptoms may help them to understand
38
39 their condition better and thereby better cope with their illness. Communicating symptoms in
40
41 an effective way that can quickly alert healthcare professionals to their discomfort is an
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43 empowering process that will make them feel secure in knowing that they have strategies that
44
45 give them the possibility to communicate with somebody who will assist them to achieve
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47 symptom relief¹⁸.
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53 Although validated patient self-report instruments exist for some symptoms healthcare
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55 professionals seldom use these in clinical practice¹⁷ furthermore most paediatric conditions
56
57 lack a validated symptom assessment tool. What is missing from the clinical toolbox is an
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3 instrument that assesses the intensity of symptoms in a simple, valid and reliable way¹⁹. One
4
5 of few symptoms that is assessed in clinical practice is pain intensity. Smeland et al. (2018)
6
7 found that, overall, pain was assessed using a validated tool in 19% of the children in post
8
9 anaesthesia care; this fell to 9% in children aged <5 years old¹⁷. An explanation for this could
10
11 be either that these instruments do not exist or that they are difficult to use, interpret or
12
13 unreliable. Healthcare professionals prefer to rely on personal judgement and experience
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15 with the patient and family²⁰ and therefore the measurement process must contribute to this
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17 and not try to replace it. The use of an instrument that focuses on a single symptom, for
18
19 example pain intensity, does not adequately capture the overall experience of the child and
20
21 can be considered a restrictive application. Novel assessment tools that give a broader
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23 description of symptoms are therefore needed in order that the child can fully communicate
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25 their experience. Novel assessment tools that give a broader
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27 description of symptoms are therefore needed in order that the child can fully communicate
28
29 their experience.

30 31 32 33 *Distress in children*

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35 The term "distress" refers to a multifactorial unpleasant emotional experience that can be
36
37 described as a combination of fear, anxiety, and pain²¹. The relationships between these
38
39 factors are complex, and the experience of distress is based on interactions between
40
41 "genetically linked behaviour patterns, temperamental predispositions, normal developmental
42
43 fears, parental psychopathology, and discrete learning experiences"²². Distress in this study is
44
45 defined as an experiential response and sensation of the mind associated with negative
46
47 emotions that appear when a situation is fearful or impossible to manage from the perspective
48
49 of the child. Distress can be a consequence of insufficient symptom relief, and self-reported
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51 distress is a global assessment that reflects the child's experience of the success of symptom
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53 relief. It is important to evaluate the distress in children undergoing cancer treatment and to
54
55 find strategies for the measurements of symptoms/emotions that are reliable and valid for this
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3 purpose. It is known that acute stress activates the hypothalamic–pituitary–adrenal (HPA)
4 axis and the sympathetic nervous system (SNS), as well as the hypothalamic–pituitary–
5 gonadal (HPG) axis²³⁻²⁵. For example, plasma cortisol concentration is an established stress
6 (energy mobilization) indicator that is known to react within minutes after the onset of stress
7 exposure. Estradiol is on the other hand an anabolic hormone, which protects against adverse
8 effects of stress.
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19 *The medical scenario within which PicPecc will be tested*

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21 The drugs used to treat children with cancer can lead to several negative side-effects, e.g.,
22 children undergoing cancer treatment frequently report nausea and vomiting and other kind of
23 distress²⁶. One of the drugs that is used in cancer treatment is methotrexate which is one of
24 the most effective medications in the treatment of acute lymphoblastic leukaemia (ALL) in
25 children²⁷. High-dose methotrexate is used world-wide and has been included as part of the
26 Nordic Society for Paediatric Haematology and Oncology acute lymphoblastic leukaemia
27 treatment protocols since 1981²⁸. Furthermore, the treatment is given according to a strictly
28 detailed Nordic and European schedules, i.e., clinical conditions have been well established.
29 For these reasons, treatment with high-dose methotrexate has been chosen as the medical
30 context within which the effect of the use of PicPecc tool will be evaluated from a person-
31 centred perspective.
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49 The primary aim of the project is to investigate whether a person-centred communication
50 intervention through the use of the PicPecc digital communication tool for children
51 undergoing cancer treatment decrease the children's symptom-related distress in general. A
52 secondary aim is to investigate the process of implementing person-centred communication
53 through the use of the PicPecc tool.
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3 *Main research question:*
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5 Does adding the PicPecc tool decrease distress (measured on an 11-point numeric rating scale
6 (NRS) (0 [no distress] and 10 [worst possible distress]) in children with ALL, aged 5-17
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8 years, who undergo high-dose methotrexate treatment?
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15 *Secondary research questions:*
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- 17 (i) Does the application of the PicPecc tool, increase person-centredness (measured
18 on VCM (Visual CARE Measure) in children with ALL, aged 5-17 years, who
19 undergo high-dose methotrexate treatment?
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26 (ii) Does the application of the PicPecc tool, alter stakeholders' perspectives in a
27 positive direction towards person-centred communication?
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33 *Hypothesis*
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- 35 (i) Children undergoing cancer treatment will experience lower distress levels, when
36 they can report their holistic symptoms in a system created using universal design
37 principles (i.e. the PicPecc tool with pictorial support) than will children with
38 standard healthcare communication opportunities (the primary outcome). In
39 addition to a decrease in self-reported stress levels there will also be a decrease in
40 neuropeptides, neurosteroids and peripheral steroids for stress and pain.
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51 (ii) Person-centred care is enhanced, through enabling children to proactively assess
52 their symptoms from a holistic perspective and communicate these to their
53 healthcare providers within an enhanced communication framework (i.e. using the
54 PicPecc tool).
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Methods and analysis

Study design

The Medical Research Council's key principles and actions for development and evaluation of complex interventions^{29 30} guided the intervention development and the research design. In a hybrid design, both the effects of the intervention and the implementation process will be evaluated³¹. Relevant care situations are selected³² where highly standardized care procedures are used and where there are a range of different situations where children struggle with symptoms. To facilitate the effect evaluation, the children will participate in a crossover design study where they are their own controls (Fig 1). The study design follows the SPENT 2019 checklist for clinical trials³³.

The development of the PicPecc tool follows established guidelines³⁴ and was based on the theoretical framework of person-centred care⁴, on published systematic reviews⁹ and on systematic reviews conducted within the project on assessment tools for nausea³⁵, and anxiety³⁶. Children with cancer, their legal guardians and healthcare professionals have been involved throughout the development process. The study protocol outlined here pertains to the evaluation and implementation phases.

Insert figure 1

Participants and units

Context and setting

In Sweden, approximately 350 children are diagnosed with cancer each year. The treatment of childhood cancer is conducted at six childhood cancer centres and at regional hospitals³⁷.

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3 Three of these childhood cancer centres and five regional hospitals in Sweden will participate
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5 in the study.
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10 Selection criteria

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12 Inclusion criteria are children diagnosed with ALL, between 5 and 17 years of age whose
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14 treatment-plan includes at least two treatments of high-dose methotrexate. The child needs to
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16 have a cognitive level of at least five years (i.e., to be able to understand an NRS³⁸). The
17
18 child's understanding of an NRS will be tested before inclusion based on a situational
19
20 judgment test which involves a realistic, hypothetical scenario about a child who fell from a
21
22 tree. The child will be asked to assess pain using the NRS. This situational judgment test has
23
24 previously been validated to discriminate positive and negative emotions³⁹. Exclusion criteria
25
26 are children 0-4 years, no verbal assent from children unable to read, scheduled to undergo
27
28 only one high-dose methotrexate treatment.
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35 The inclusion criteria for legal guardians will be that their child has undergone the high-dose
36
37 methotrexate treatment and has used the PicPecc tool. In addition, legal guardians will need
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39 to be at the hospital during the treatment.
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44 The inclusion criteria for healthcare providers will be that they are responsible for the
45
46 children's care during the high-dose methotrexate treatment when the children use the
47
48 PicPecc tool.
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53 Method of recruitment

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55 The recruitment is planned to start in the beginning of 2021. The surveyed children
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57 participate in data collection twice, once as a control (A) and once at the time of symptom
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3 reporting and initial use of the communication tool PicPecc (B) (Fig. 1). Children with cancer
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5 aged 5-17 years old, legal guardians and healthcare professionals at three childhood cancer
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7 centres and five regional hospitals in Southern Sweden will participate in the study. Each
8
9 year approximately 175-200 children get cancer in Southern Sweden, and about a third of
10
11 these children receive a diagnosis of ALL. At the three childhood cancer centres and at the
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13 five regional hospitals included in this study, approximately 25 of these children will fulfil
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15 the inclusion criteria for this study each year.
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21 Healthcare providers at each of the units will be interviewed. The nurse and/or nurses that
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23 initiate and conclude the high-dose methotrexate treatment, will be invited to a semi-
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25 structured interview.
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30 Consent process

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33 Legal guardians of children below 15 years of age with ALL who are scheduled to receive
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35 high-dose methotrexate treatments will be informed about the study by a physician or a nurse,
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37 included in the research group. The legal guardian will receive written information, and the
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39 child will be given text and picture-based information. Upon consent from a legal guardian,
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41 child assent is obtained verbally and in writing if the child can read. Older children (aged 15
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43 years or above) will give written consent themselves. In Sweden, children between 15 and 18
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45 years can provide written informed consent themselves if they are assessed to have the level
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47 of maturity and capacity to understand the consequences of participation.
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53 Randomization

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56 The participants will be allocated codes in a consecutive order; the code is randomly assigned
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58 to either the intervention phase (B) or control phase (A). Participating cancer units will be
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3 given the solution to the randomization code once the codes have been allocated to the
4 participants. The participants will only have access to the PicPecc tool during the intervention
5 phase. There will be a period of at least two weeks between the end of the first intervention
6 period and the start of the next methotrexate treatment. This provides an adequate washout
7 period between the intervention (B) and the control phase (A) for any behaviour change to
8 revert to previous patterns. Following the transtheoretical model⁴⁰ habitual behaviour change
9 related to health is a process involving a number of stages which takes time to complete
10 successfully. Where support for change is removed early in the process the individual will
11 quickly revert to previous habituated behavioural patterns. We are confident therefore, that
12 the intervention will have no residual effects on the control phase.
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29 *Measures and materials*

30 I) Impact evaluation

31 We consider a difference of 15% to be a meaningful difference in score average between T0
32 and T2 (48 hours); this is represented by a difference of approximately 1.5 units on the NRS
33 (0-10) of distress, when comparing users of the PicPecc tool to control subjects. The estimate
34 of standard deviation is based on unpublished data of 11 to 12-year-old girls' self-reports⁴¹.
35 Based on an expected standard deviation of 2.9 (and a power of 0.8), it is necessary to include
36 at least 32 participants. With a dropout rate of approximately 20%, 20 participants in each
37 group, i.e., 40 participants will be included in the study.
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51 In both the control (A) and intervention phases (B), the data collection follows the test-period
52 outline in Figure 2. Assessment of distress will be made at time points T-1, T0, T1 and T2.
53 T3 is an interview to evaluate the implementation process. Primary outcome is the difference
54 in delta T0 and T2 between control and intervention phases. The time points are linked to the
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3 schedule for the methotrexate treatment to avoid extra blood sampling. The time points will
4
5 also facilitate the evaluation between before and after treatment, with the objective to
6
7 evaluate differences in symptoms, with and without the PicPecc tool (Fig. 2).
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12 *Insert figure 2*
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17 Primary outcome:

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19 The change in the primary outcome variable (distress) from baseline (T0) to 48 hours after
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21 treatment start (T2) measured on an 11-point NRS (0 [no distress] and 10 [worst possible
22
23 distress])^{42 43} will be compared between the control and intervention phases. Self-reported
24
25 distress (NRS-11) will also be collected four hours before high-dose methotrexate (T-1), and
26
27 after 24 hours (T1) (Fig. 2) in order to establish within subject variation.
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31 Secondary outcomes:

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33 1. Blood samples will be collected and steroid levels in plasma will be monitored. Pain
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35 and steroid levels in blood: neuropeptides, neurosteroids and peripheral steroids will
36
37 be collected before start (T-1 and T0) of the high-dose methotrexate treatment, 24
38
39 hours after start (T1), and 48 hours after start (T2). Since blood-drawing procedures
40
41 are part of routine monitoring of cancer care, a small sample of the blood will be
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43 obtained for this research, with no additional needle pricks required. Steroids are
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45 measured in this study using LC-MS/MS and SFC-MS/MS methods⁴⁴. It is not
46
47 possible to distinguish between different types of stress, but the design includes the
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49 evaluation of two indicators of stress response, firstly, biological (measured by
50
51 biomarkers) and secondly, perceived (self-reported). Since the same individual is
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53 assessed before and after the chemotherapy, both with and without the PicPecc tool, it
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55 is possible to evaluate the effect of the PicPecc tool on intervention-related stress.
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2. Self-reported person-centredness. This is evaluated on the VCM⁴⁵, which will be collected 48 hours after the start (T2) of the high-dose methotrexate treatment. The VCM provides the legal guardians of children <7 years old (VCM 10Q-Legal guardians), children aged 7-11 years (VCM 5Q) and adolescents aged 12 years and over (VCM 10Q) the opportunity to report their experiences regarding both the meeting with the healthcare professional and their participation in decision related to healthcare⁴⁵.
3. Frequency of assessments of symptoms with the PicPecc tool. In-app assessment levels will be recorded during the intervention phase, and during the control phase a checklist will be used (e.g., frequency of symptom assessments T0-T2 (Fig 2)).
4. Drug consumption for all types of symptom relief. These data will be collected from the patients' medical records.

II) Process evaluation

After each intervention, experiences of care during the treatment are explored in individual semi-structured interviews (T3) with all participating children, their legal guardians and the healthcare professionals involved in the children's care. The objective is to illuminate the experiences of using the PicPecc tool from the perspective of the participating children, their legal guardians and the healthcare professionals. The interviews will be thematically analysed following the procedures of Braun and Clarke⁴⁶ to give an understanding of how the PicPecc tool was used during the intervention.

Numeric data regarding when and how often the children used the PicPecc tool, will also be collected.

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3 The semi-structured interviews will follow an interview guide adapted for the child according
4 to age and maturity. The questions will also be provided with pictorial support according to
5 the concept of universal design (Supplementary file 1). The child and the legal guardian are
6 interviewed separately. The aim is to interview both the child and their legal guardian
7 however, if either of them is unwilling or does not fit the criteria the other (child or legal
8 guardian) will be invited to participate on their own.
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19 *Intervention*

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21 In the intervention phase the child will use the PicPecc tool before and during high-dose
22 methotrexate treatment for communicative support to assess their symptoms and emotions.
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24 The PicPecc tool is used in a phone or a tablet computer; delivered via an iOS or Android
25 platform. The development of the PicPecc tool is presented elsewhere³⁴. The PicPecc tool is
26 based on a child-centred assessment approach, and the goal is to adapt the assessment to the
27 child's age, maturity, diagnosis, language ability, and cultural background. All sections of the
28 PicPecc tool will contain pictures, text, and sound. The PicPecc tool includes an assessment
29 scale, which is designed as a thermometer. The thermometer is graded from zero (green) to
30 ten (red). Each level of the scale is also symbolised with a face that shows the intensity of
31 each symptom and/or emotion. The result of the assessment is visualized as a facial
32 expression and colour that represents the intensity of the symptom and/or emotion (i.e.,
33 anxiety, appetite, fear, how I'm feeling today, nausea, pain, and sleep). In addition, the
34 PicPecc tool has a body outline without any markings on which the child can indicate the
35 location of the symptom and/or emotion, pictures for the type of symptom and/or emotion; as
36 well as open questions where the child can write narratives about symptoms and/or emotions.
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38 The child receives visual feedback from the app and directly from healthcare professionals
39 participating in the intervention, on their reported assessments made with the thermometer.
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3 The child can follow the assessments on an hourly, daily or weekly basis. The PicPecc tool
4 also includes a personal avatar to represent the child. Using the avatar the child can make
5 choices of the avatar's gender, skin and hair colour, and its facial expressions thus
6 contributing to the inclusiveness of the PicPecc tool by providing racial and gender diversity.
7
8 The avatar will be linked to the child throughout all the assessments. In addition, in order to
9 enhance interaction with the tool the design of the app includes a gamification element, e.g.,
10 the child will get a reward in the form of a pet when he/she has assessed the symptoms and/or
11 emotions (Fig 3-5). The child is encouraged with a reminder in the PicPecc tool to assess the
12 symptoms and/or emotions twice daily (in the morning and in the evening). The child can in
13 addition assess his/her symptoms and/or emotions more frequently with the PicPecc tool, e.g.,
14 if he or she prefers to do so.
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40 *Insert figure 5*

41 42 43 44 *The implementation of a person-centred approach in both phase A and phase B*

45 The implementation strategies of person-centred communication consist of two components:

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47 (i) A person centred workshop for the paediatric oncology teams about enhanced
48 symptom communication;
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50 (ii) One member of the research team will be assigned to coach their colleagues in each
51 of the clinical departments on the person-centred approach. They will support the
52 implementation of the intervention and be responsible for data collection.
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6 i. Workshops with paediatric oncology teams

7 Paediatric oncology teams will be invited to a workshop which will scrutinize and discuss
8 communication issues based on five questions. These questions will be 1) how
9 communication, based on a person-centred approach, can be implemented in clinical practice
10 in child healthcare? 2) Can universal design facilitate the implementation of person-centred
11 care for children? 3) What are the negative effects of distress for the child? 4) What are the
12 strategies to decrease distress, e.g., symptom management? 5) How can the PicPecc tool
13 enhance person-centred communication, and how it can be used in clinical practice? (Fig. 6).
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26 *Insert figure 6*
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31 ii. Clinical coaches to support the implementation of the intervention

32 One coach in each of the clinical departments will support the implementation of the
33 intervention. The coach will be responsible for facilitating education and support for their
34 colleagues in the clinical department. In addition, the coaches will also be responsible for
35 data collection. The coach in each clinical ward will get support with the research process
36 from the research group.
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47 *Procedural fidelity*

48 The procedural fidelity will be evaluated in each phase. The coach will (a) monitor the
49 occurrence of relevant variables, (b) provide documentation that the experimental conditions
50 occurred as planned, (c) provide support to practitioners about the use of the interventions.
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58 *Data analyses plan*
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Effect evaluation

We expect the intervention to be superior to the control in terms of the health outcome assessment (NRS-11). We also expect that there will be a difference between pre methotrexate treatment (T-1, T0) and methotrexate treatment (T1, T2) in both intervention and control phases. Therefore, we will test the null hypothesis that there will be no change in any of the measurements between the pre methotrexate treatment (T-1, T0) and methotrexate treatment (T1, T2) nor between intervention and control phases. A p value of < 0.05 will be considered as statistically significant. Categorical data will be descriptively analysed by frequency distributions and percentages. The paired sample t-test will evaluate the difference between two sets of assessments and effect size⁴⁷. Data will be analysed with IBM SPSS Statistics 25 (New York City, USA).

Process evaluation

The qualitative data analysis will be driven by interpretive description methodology, and the analysis will follow a mixed-methods research design, i.e., a convergent design, with concurrent timing where qualitative and quantitative data are independent of each other. The goal is to disclose experiential and contextually shaped knowledge⁴⁸. The qualitative data will be interpreted, and the analysis will lead to the identification of a set of themes which describe the child's experience of using the tool. The quantitative data about the frequencies of the participants' use of the PicPecc tool will be analysed with descriptive statistics, which will then be integrated with the qualitative analysis to facilitate a deeper understanding of how the children use the PicPecc tool. Finally, an interpretation will be conducted between qualitative and quantitative data⁴⁹.

Patient and public involvement

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3 Children with cancer, legal guardians and their healthcare professionals have been involved
4 in the development of the PicPecc tool³⁴. Healthcare professionals have been involved in the
5 development of the hybrid design, in order to optimise the feasibility of the study.
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10 11 12 *Data monitoring committee*

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14 The study will have an external expert panel that will be responsible for checking the quality
15 of the data in the study. The expert panel will also evaluate ethical issues that emerge during
16 the study period.
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23 24 **Ethics and dissemination**

25 26 *Ethics*

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28 Ethical approval was obtained from the Swedish Ethical Review Authority (ref 2019-02392;
29 2020-02601; 2020-06226) for the planned studies. Children are a vulnerable group since
30 adults have a power relationship with the child, the child with cancer is in a difficult life
31 situation, and the child is expected to share personal stories. All data collection is carried out
32 during hospital treatment, and all ordinary management and safety mechanisms are in place.
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34 If complications occur in conjunction with the intervention, these are reported at the usual
35 clinical rounds and will be managed according to the ordinary routines.
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47 The children and their legal guardians will be informed about the purpose of the study. The
48 information to participants states that all participation is voluntary and will not adversely
49 affect the child's health-care, and that it is possible to withdraw consent without explanation
50 or any negative consequences on their treatment and care. All data will be kept confidential,
51 and it is only the research group that has access to the data. The results will not reveal the
52 identity of the participants. Research with children, legal guardians and healthcare
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professionals requires an ethics committee approval, written consent from the child and the legal guardian and verbal assent from children unable to read.

Dissemination

Research findings will be presented at international cancer and paediatric conferences, published in scientific journals and publications for children with cancer and their legal guardians. The results will also be available for professional training purposes.

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40 Methodology: S.N., J.B., J.C., M.S., J.Ö; Project administration: S.N.; Supervision: S.N.,
41 J.B., J.C, M.S., J.Ö.; Visualisation: S.N.; Writing the original draft: S.N., A.W., J.B., J.C.,
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10 11 12 **Figure Legends** 13

14
15 Fig. 1. The cross-over design with two study groups will participate in two phases as related
16 to the Nordic and European study protocols in Sweden for treatment of children with high-
17 dose methotrexate. All methotrexate treatment sessions take a similar amount of time for the
18 child. The intervals between each of the methotrexate treatments will be controlled by each
19 child's treatment plan and may vary between 3 and 6 weeks.
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28 Fig. 2. Data collection time points and variables in both the control and intervention phases.
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33 Fig. 3. The PicPecc tool consists of an avatar and pets that the child can win through
34 interaction with the reporting process.
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40 Fig. 4. Reports are made by using a thermometer for assessing symptoms and emotions.
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44 Fig. 5. The child receives feedback on the assessments in the form of diagrams showing the
45 results of the latest days or weeks.
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51 Fig. 6. The questions for the workshops with communication and symptom management.
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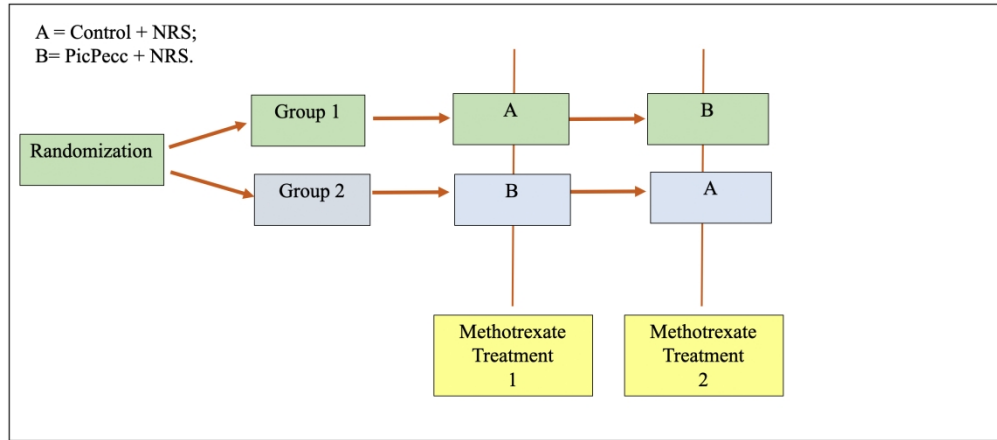


Fig. 1. The cross-over design with two study groups will participate in two phases as related to the Nordic and European study protocols in Sweden for treatment of children with high-dose methotrexate. All methotrexate treatment sessions take a similar amount of time for the child. The intervals between each of the methotrexate treatments will be controlled by each child's treatment plan and may vary between 3 and 6 weeks.

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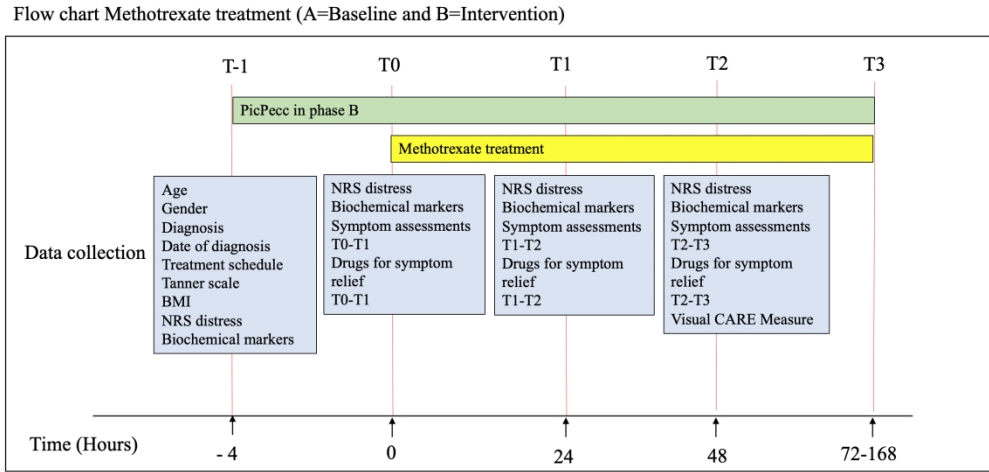


Fig. 2. Data collection time-points and variables in both the control and intervention phases.

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Figure 3. The PicPecc tool consists of an avatar and pets that the child can win through interaction with the reporting process.

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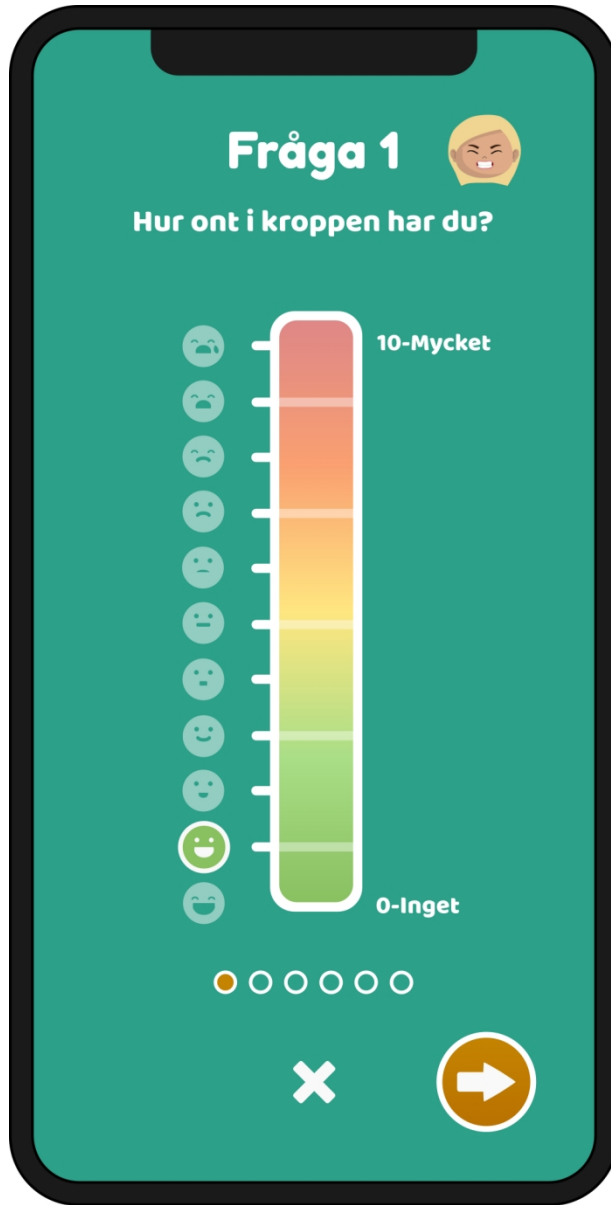


Figure 4. Reports are made by using a thermometer for assessing symptoms and emotions.

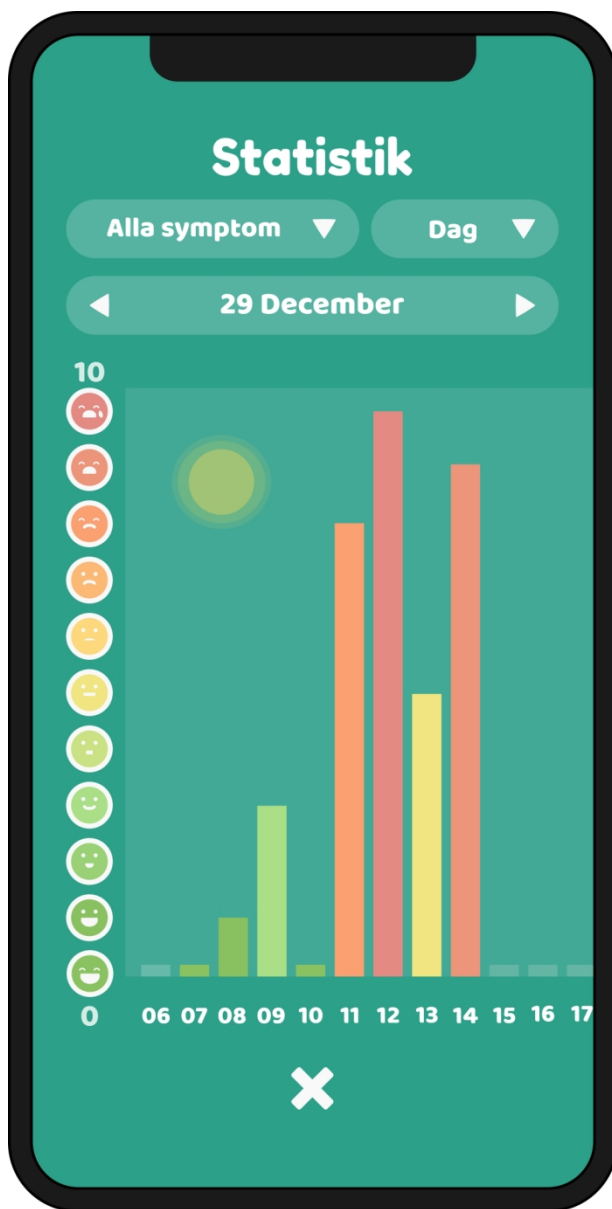


Figure 5. The child receives feedback on the assessments in the form of diagrams showing the results of the latest days or weeks.

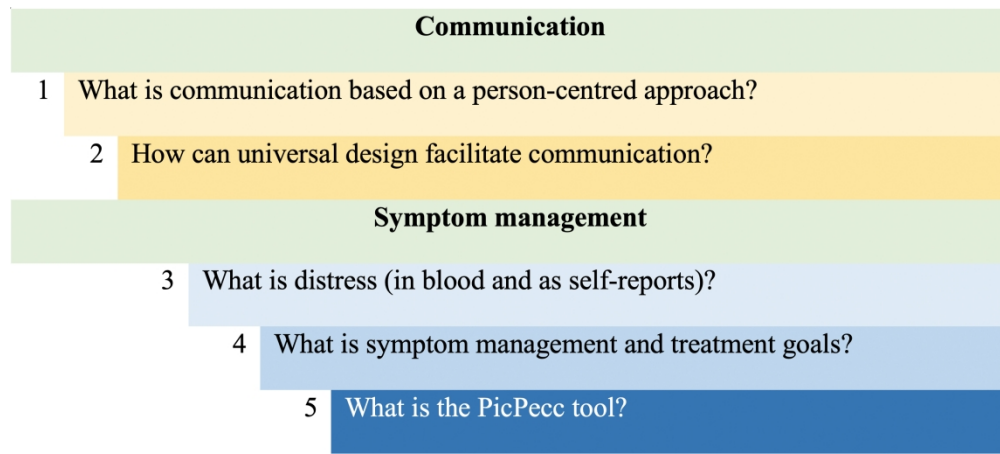


Fig. 6. The questions for the workshops with communication and symptom management.

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3 Supplementary file 1. Interview questions in the process evaluation
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5 Main questions to the child:
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7 Tell me about your thoughts about getting your treatment.
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9 Did the healthcare professionals listen to your wishes?
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12 Tell me about a situation when you got support.
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14 Main questions to legal guardians:
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16 Tell me about your child's care.
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18 Did the healthcare professionals listen to you and your child's wishes?
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21 Tell me about a situation when your child got support.
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24 Main questions to healthcare professionals:
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26 Tell me about your experience of caring for the child.
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28 Do you think that the child felt listened to?
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31 Tell me about a situation when the child got support.
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