

## MIXED METHODS SYNTHESIS OF RESEARCH ON CHILDHOOD CHRONIC CONDITIONS AND FAMILY

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### SPECIFIC AIMS

An estimated 18% of children from birth to 18 years of age have a chronic condition requiring the use of more health-related services than other children [1]. A substantial percentage of these children have a chronic physical condition (CPC) such as asthma or diabetes putting them at increased risk for adjustment problems related to their emotional and behavioral development and functioning [2-4]. Research findings on the intersection of family life and childhood CPCs consistently point to the contribution of family variables to child adjustment, and to the conclusion that families and family members other than the affected child also are at increased risk for poorer functioning [4-10]. Still unknown, however, are the factors that prevent, ameliorate, or increase risk for children and families and how adjustment and functioning vary over time in these children, families, and family members. Knowledge of these risk and resistance factors will provide an evidence base for developing interventions that support optimal child, family, and family member outcomes [11, 12].

Prior reviews have documented the reciprocal nature of child and family responses, but their scope has been limited to selected aspects of family response [8, 10], conditions [9], or time periods [4], and to studies with only certain research designs (e.g., only RCTs, only qualitative studies). These delimitations have posed a barrier to addressing important questions regarding the relationship of child development, disease course, family structure, and other factors to family response and child health outcomes. Yet, these questions must be answered to develop patient-/family-centered interventions that take into account the unique needs and characteristics of children and families. Lauver and colleagues [13] noted that patient-centered interventions, regardless of form (personalized, targeted, tailored, individualized), should be theoretically or empirically grounded and customized based on the healthcare professional's assessment of patient characteristics related to a particular health concern. Discussing the modest effects of interventions to enhance child and family adaptation to chronic conditions, Wallender and Varni [4] concluded that a likely explanation was that rather than being patient/family-centered, they were applied equally and were not customized to take into account how characteristics of the condition intersected with individual and family adjustment. **Others have identified the importance of also taking into account socio-cultural factors when developing interventions to promote optimal child and family adaptation to a CPC** [11, 14].

The significant contributions of research synthesis studies to the scientific basis for practice increasingly have been recognized [15-17]. Especially notable are the call to include all relevant empirical studies regardless of their methodological pedigree, the development of novel approaches for synthesizing methodologically diverse findings, and collaboration with key users of findings of research synthesis studies to optimize their relevance and usability [18, 19]. The proposed research synthesis addresses the limitations of prior reviews by fully mining the body of research addressing family life in the context of childhood CPCs via the use of state-of-the-art methods to integrate the findings from this research in collaboration with family researchers and clinical decision makers. The overall objective of the proposed study is to synthesize findings from empirical research addressing the intersection between family life and childhood CPCs. Bayesian meta-analysis and realist synthesis methods [18, 20] will be used to:

- (1) **Map the relationships found among condition management and control; functioning of the affected child, parents, and siblings; family life and functioning; family relationship with the healthcare system; and individual and family demographics.**
- (2) **Explain how these factors operate together to produce variations in child and family outcomes.**
- (3) **Describe the nature of interventions directed to families of children with CPCs and their effects on child and family outcomes.**
- (4) **Examine factors mediating and moderating intervention effects.**

The outcomes of the proposed study will be (a) evidence summaries addressing each of the four specific aims and (b) theoretical integrations of findings that address the strengths of families with children with CPCs, the problems these families confront, and the rationale for interventions to enhance these strengths and address these problems. Study findings will be disseminated in forms

accessible to and usable by both researchers and clinical decision makers. The proposed study addresses the National Institute of Nursing Research emphasis on Improving Quality of Life through support for research that generates knowledge of self and family management of chronic conditions.

## RESEARCH STRATEGY

### Significance

The significance of the proposed research synthesis study lies in its taking full advantage of the knowledge gained from existing studies to close gaps or offset deficits in research on the intersection of family life and CPCs. Although prior reviews have established the reciprocal nature of child and family response to CPCs, they also point to the imprecision of current understanding of factors contributing to variations in child and family adjustment and functioning over time [4, 5, 8-10, 21-22]. Noting the importance of developing patient-centered interventions to support optimal child and family adaptation, reviewers have offered remarkably consistent recommendations for the direction of future research. They have called for studies to further explain families' and children's variable responses to CPCs. They have pointed to the need for longitudinal studies that take into account the nature and course of the chronic condition, the child's and family's developmental phase, and demographic variables, such as gender, family structure, and ethnicity. The comprehensive research synthesis study we propose will address the concerns and recommendations of reviewers by fully mining the current literature to provide a more precise understanding of factors that need to be taken into account when developing interventions for children with CPCs and their families. Consistent with Lauver and colleagues' [13] definition of patient-centered interventions, the study we propose will advance the theoretical and empirical basis for customizing interventions.

**The factors that account for variation in child and family outcomes have yet to be fully delineated.** The proposed study builds on the compelling body of research that points to the pivotal contribution of family processes to child adaptation to CPCs and the reciprocal nature of family and child response [8, 14, 23-26]. For example, in a review of 57 studies of children's psychological adjustment to a chronic condition, Drotar [3] found that in 53 of them, at least one measure of child functioning was significantly related to family/parental functioning. Other major reviews [2, 4, 27] also have shown that family functioning was a significant predictor of child adjustment. The family functioning variables of conflict, cohesion, and expressiveness consistently have been shown to mediate children's adaptation to a chronic condition [5, 23-24, 26, 28]. **The family-specific demographic variables of socioeconomic status, caregiver marital status, and number and ages of children in the home also have been associated with the quality of child and family adaptation [8].** These reviews provide important glimpses into the contribution of family characteristics to child outcomes, but reviewers also noted their inadequacies with regard to providing the specific knowledge needed to customize interventions.

A compelling body of evidence also exists that childhood chronic conditions affect family functioning as well as the functioning of individual family members [2, 29-30]. Wallander [4] concluded that parents (especially mothers) of children with CPCs were at increased risk for adjustment problems **and Herzer and colleagues [8] found that across studies, approximately one quarter of families of children with CPCs show areas of poor family functioning.** Reviewers have found that parents of children with cancer are especially vulnerable to psychological distress, including post-traumatic stress syndrome [29-31] with the degree of distress varying over the course of the illness. Other studies have addressed the psychosocial adjustment of siblings of children with a CPC, and reviews of these studies [2, 32-33] present a mixed picture of sibling adjustment. A meta-analysis of 51 studies of siblings of children with varied chronic conditions showed a small negative effect on psychosocial functioning compared to controls or a comparison group [34]. On the other hand, reviews [33, 35] of studies of siblings of children with cancer identified both positive and negative outcomes. Although reviewers [2, 32] identified possible moderating variables such as condition type and intensity of treatment regimen, they noted the absence of a definitive understanding of the nature and correlates of sibling response to CPCs.

With regard to family system response to a member's chronic condition, Knafl and Gilliss [22], in their review of 73 studies (ill member a child in 45 of these studies), found that the research presented a "mixed picture of the impact of chronic illness on family life" (p. 185), with some researchers reporting good and others reporting poor family functioning. Like other reviewers, they reported that families of children with cancer appear to be

particularly at risk for poor functioning. With the exception of cancer, understanding of the relative impact of specific conditions on family functioning and the health of individual family members is limited [2] **with some studies involving comparisons across conditions indicating differences and others, no difference [8]. Other reviewers have concluded that the events surrounding the diagnosis can be especially pivotal and may influence ongoing interactions with healthcare professionals and child and family adaptation [36-38].** Similar to reviews of the impact of CPCs on children, those addressing family and family member outcomes have emphasized the limitations of the current evidence base for practice and the need for studies that take a longitudinal perspective and address the relative contribution of a broad array of demographic (e.g., ethnicity, family structure) variables [2, 4, 7, 10, 32]. The research synthesis study we propose is in keeping with recommendations of prior reviews and will make significant contributions to further explaining how factors related to the child with a CPC, the condition itself, and family are linked to different approaches to management and to different outcomes for both these children and their families. This level of specification is needed to develop interventions that take into account the unique **characteristics and** circumstances of diverse families experiencing different chronic conditions at different points in their development.

A critical barrier to progress in the field has been that primary family studies are highly constrained in their capacity to study the family system over time. In a single study, at best, only so many members in individual families can be studied around only so many events or experiences at only so many points in time. Family research has been focused on eliciting data from individual family members (one or multiple members of the family system) and family researchers have noted the conceptual and analytic challenges inherent in combining these data to convey a picture of the family system [39-44]. As described in the Approach section of this proposal, the mixed methods design we propose addresses these constraints by including findings from a large sample of methodologically diverse empirical studies to reveal how the management and outcomes of a child's CPC vary over time for the child and family.

**To customize interventions, an understanding is needed of how condition management and control vary across chronic conditions.** CPCs present children and their families with common and condition-specific challenges related to condition management and control. Many researchers have advocated taking a non-categorical approach that is focused on the common challenges CPCs present for children and their families rather than a categorical approach focused on the impact of specific diagnoses [4, 45-46]. Advocates of a non-categorical approach have developed several frameworks that highlight generic dimensions of the chronic illness experience [47-50]. Despite some differences, all these frameworks identify groupings of condition types that vary in terms of disease course, functional limitations, prognosis, and/or visibility. The proposed study may identify other generic aspects of family response to CPCs. Researchers also have taken a categorical approach and studied children with specific diagnoses and their families. Authors of prior reviews have identified a need to understand better the common versus unique challenges of different conditions [2-4, 34]. Our proposed research synthesis study will include analyses of studies focused on a single condition (categorical) and studies including multiple conditions (non-categorical) in order to differentiate psychosocial challenges common across CPCs from those that are condition-specific. Findings from the synthesis also will yield information about when it is appropriate to base interventions on primary findings from the broader base of evidence on childhood CPCs versus condition-specific findings.

**To advance evidence-based practice, an understanding is needed of factors that account for the effectiveness of family-focused interventions.** Along with recognition of the reciprocal nature of child and family response to CPCs has been growing interest in the development and testing of family-focused interventions [51-54]. Reviews of family-focused intervention research have provided evidence of their effectiveness with regard to condition knowledge [51-52], condition management [51-52], health outcomes [54], and improved family/family member functioning [51-52]. Yet, reviewers have identified considerable variation in the effects of interventions across families and the need for further research to explain the reasons for that variation. The proposed study will allow us to distinguish factors that moderate the effects of interventions, causing variations in management and outcomes: factors related to condition, individual, and family system. To date, much of the research on family-focused interventions has been directed to families in which a child or adolescent has asthma, diabetes, or cancer [51, 53] and has been limited with regard to family structure and the demographic characteristics of study participants. Because of these limitations, reviewers have concluded there is a need to develop interventions that target a much broader array of conditions and families, but have noted as well the inadequacy of the current evidence base for doing so [51-54]. Greater understanding of moderators will allow us to identify intervention strategies that are likely to be effective across a broad range of children, families, and conditions. The study also

will contribute to understanding of the mechanisms (or mediators) by which interventions have their effect, allowing us to differentiate those components of an intervention that should be maintained with fidelity from those that can be adapted.

**Mixed research synthesis studies can address the gaps, limitations, and inconsistencies in knowledge of family life in the context of childhood CPCs in ways not possible in individual primary studies.** The body of knowledge in the field, and not the individual study, is now increasingly viewed as the optimal source of evidence for guiding clinical practice and intervention development [15-17]. Also better understood are the contributions of different kinds of research to the development, testing, and dissemination of interventions [17, 19, 55] Although knowledge synthesis efforts in health care to date have been focused on randomized controlled trials, or on other kinds of studies differentiated by method, investigators are now urged to broaden the array of study designs included in their research synthesis efforts. Methods are now available for conducting such mixed research synthesis studies [56], including those further and newly developed by PI Sandelowski and co-I's Leeman and Crandell.

Research synthesis allows the multiple angles of vision and voices constituting "family" [57] to be configured, or placed in relation to each other. In their discussions of the methodological challenges of family research, however, researchers have yet to take full advantage of the potential contributions of mixed methods reviews of methodologically diverse research findings for advancing family research and practice. Research syntheses are by definition empirical and/or theoretical assemblages of diverse information about different aspects constituting a domain of study. Syntheses of research findings from a comprehensive collection of primary studies focused on the family can therefore get closer to capturing the multiple multiples constituting "family." Applying state-of-the-art mixed research synthesis techniques, researchers can, for example, take findings about mothers or fathers or affected children, including those from studies exclusively focused on one group alone, and place them in relation to each other and to findings about outcomes associated with particular phases in the trajectory of specific chronic conditions. Findings from cross-sectional studies focused on different points in the trajectory of chronic conditions can be configured into longitudinal profiles of events and experiences that reflect how child and family responses and outcomes unfold over the course of the child's and family's development. Research syntheses are arguably the best way to advance knowledge about the intersection of family life and chronic CPCs as they capture the dynamic mosaic of child, family, and condition factors that shape outcomes over time.

### **Innovation**

The proposed research is innovative in its topical, conceptual, and methodological scope (i.e., inclusive of a wide range of methodologically diverse family studies focused on different aspects of family life in the context of childhood CPCs); capacity to address key research problems in family studies (e.g., advantages of categorical versus non-categorical approaches, lack of attention to development and family background); and application of state-of-the-art methods for conducting mixed research synthesis studies. The proposed research is innovative too in its intent to develop sets of evidence summaries and theoretical integrations of findings that researchers and clinicians can choose from and use as the foundation for programs of intervention research and of care delivery to improve child and family outcomes. Moreover, as we will further detail below, the proposed study is novel in its collaboration with clinical decision makers (those managing and providing direct care) to develop usable evidence syntheses targeted to clinical audiences **and professional organizations to assure appropriate dissemination of results.**

### **Approach**

#### **Preliminary Studies**

The proposed project brings together expertise in family research and mixed research synthesis. PI Knaf'l's research has been focused on family management of childhood chronic conditions with a particular interest in identifying key aspects of family response that cut across varied condition and family contexts. Funded by both public and private sources, her work has included empirical studies of families in which a child has a chronic condition [58-62] as well as theoretical [63-65] and methodological work [44, 66-68] related to the treatment of the family as the unit of study and analysis. The mixed research synthesis methods that will be used were newly or further developed by PI Sandelowski and Co-Is Leeman and Crandell in two NINR-funded studies (*Analytic techniques for qualitative metasynthesis*, R01 NR004907, 2000-2005, and *Integrating qualitative & quantitative research findings*, 5R01 NR004907, 2005-2011 [includes NCE]).

To prepare specifically for the proposed project **and working closely with an information specialist skilled**

**in advanced search techniques (co-investigator Shaw-Kokot), we conducted a “scoping” study to map the main sources and types of evidence available to address our research aims [69]. To capture English-language reports of family studies across the disciplines and worldwide, we searched the following databases: Academic Search Premier, Cumulative Index to Nursing and Allied Health (CINAHL), Excerpta Medica database (EMBASE), Educational Resource Information Center (ERIC), Family and Society Studies Worldwide, PsycINFO, PubMed, Science Citation Index Expanded, Social Work Abstracts, and Sociological Abstracts. We experimented with different combinations of search terms to ascertain which combinations would yield the highest number of relevant documents [70-71]. For example, we compared the different databases to determine which yielded the most unique relevant documents. We compared the number of relevant documents retrieved and missed when using general search terms for childhood chronic conditions (i.e., child\* or teen\* or adolesc\* or infant\* in combination with disab\* or special need\* or chronic\* or genet\*) with the number retrieved using terms for specific conditions (child\* or teen\* or adolesc\* or infant\* in combination with terms such as asthma\*, sickle cell\*, diabet\*, cystic fibro\*). **These preliminary searches of multiple databases identified approximately 900 potentially relevant research reports published between 1995 and the present and served to further refine our search strategies and targets. We also derived from this scoping review working definitions of the key concepts in this study (described below).****

**We examined a subset of reports retrieved from PubMed to further delineate study characteristics, including approximately 300 reports of qualitative and quantitative observational research and 35 reports of intervention studies published between January 2000 and June 2010. Cancer (52 reports), asthma (41 reports), and diabetes (37 reports) were the most frequently studied single conditions; the remaining reports were of non-categorical studies addressing multiple chronic conditions, and 1-20 reports each of such single conditions as cystic fibrosis, PKU, and sickle cell disease. This more detailed review resulted in the initial categorization of variables shown in Table 2 that will guide our final sample selection. Our review of the 35 intervention reports provided information concerning the effectiveness of largely psycho-educational, counseling and/or support interventions with regard to condition knowledge and management, health outcomes, and improved family/family member functioning in condition-specific (most often diabetes or asthma) and non-categorical contexts. We also searched Dissertations and Theses (via ProQuest Company) and identified approximately 200 reports of studies of family response to childhood chronic conditions completed between 2000 and 2005. We completed a forward search of publications resulting from these dissertations, and identified potentially eligible publications from approximately 24% of dissertations. Our preliminary work indicates the availability of a body of research more than sufficient for fulfilling the aims of the proposed study.**

### **Overview of Design**

To accommodate the diverse methodological pedigrees of the studies to be included, the proposed research syntheses will be accomplished by aggregation [72] using Bayesian meta-analysis [73] and configuration [72] using a realist synthesis approach [18].

Synthesis by aggregation entails the assimilation of thematically similar findings, or findings considered to indicate the same relationship or connection between two or more aspects of a phenomenon. Such findings are seen to confirm each other. Thematically similar qualitative and quantitative findings may be pooled at the subject or study levels. They may be pooled at the subject level if the numbers of subjects linked to the qualitative findings is available or can be inferred from reports [74]. The type of qualitative findings most amenable to pooling is that found in basic descriptive studies [75]. Yet, thematically similar qualitative and quantitative findings will more likely be amenable to pooling at the study level as the number of subjects linked to qualitative findings is often not available, cannot be inferred from reports, or is not relevant to the presentation of highly interpreted findings [74]. Indeed, whether minimally (basic descriptive) or highly (e.g., grounded theories, phenomenological descriptions) interpreted, qualitative findings are typically presented at the study level, with thematic and interpretive lines usually prevailing over frequency counts and within-participant or between-thematic lines comparisons prevailing over between- and cross-participant comparisons. In contrast, quantitative findings are represented as group-level statistics (e.g., odds ratio) based on subject-level information. The subject-level option entails quantizing qualitative findings, while the study-level option entails qualitzing quantitative findings [76-77]. Reviewers decide on the option likely to yield the most meaningful results with the least amount of information loss. All research synthesis projects entail such trade-offs [78].

In contrast, synthesis by configuration involves the arrangement of disparate individual findings and sets of pooled findings into coherent theoretical renderings of them. While findings must be seen as thematically similar to aggregate them, findings in configuration syntheses are conceived as thematically dissimilar (and therefore as not amenable to mathematical pooling) as they address different relationships between the same aspects of a target phenomenon or wholly different aspects of that phenomenon. Such findings are seen to complement (i.e., explain, extend, or otherwise modify) each other, as when individual and/or pooled findings are linked, even though this link was never actually empirically shown or even addressed in any primary study. Conceptual frameworks, models, and theories are primary examples of configurations in science. Configuration may be top-down, whereby reviewers use a conceptual framework or theory—drawn from the primary studies reviewed or from some other literature—to map findings with a view to establishing linkages. Configuration may be bottom-up, or a conceptual framing largely derived from examining the findings. Top-down approaches are not simply deductive as they always entail hunches derived from the data that certain concepts or models might be useful and generative ways to configure findings. Bottom-up approaches are not simply inductive as they always draw from prior understandings, theoretical leanings, and the like concerning what factors might belong together, the order in which they are arranged, and the like. Table 1 summarizes a comparison between synthesis by aggregation and configuration, including examples of methods used to accomplish each type.

**Table 1. Comparison of Research Synthesis by Aggregation and Configuration**

Synthesis by:	Aggregation	Configuration
<b>Type of integration Focus</b>	Empirical Thematically similar findings	Theoretical Thematically dissimilar individual and pooled findings
<b>Logic</b>	Confirmation via repetition of findings	Explanation, modification via coherent assembly of findings
<b>Points/direction of integration</b>	Study level Subject level	Top-down Bottom-up
<b>Process</b>	Averaging, merging	Linking, meshing
<b>End-product</b>	Pooled summary	Theory, model
<b>Methods/techniques</b>	Meta-analysis (Bayesian, frequentist) Metasummary	Grounded theory Realist synthesis Reciprocal translation, conceptual synthesis
<b>Comment</b>	Pooled findings can be configured	Configured findings cannot be pooled

### Sample (Search and Retrieval of Relevant Reports)

**Our initial guide for selecting research reports for the proposed study is the set of grouped variables shown in Table 2 derived from our scoping study and a preliminary review of a subset of the reports we identified. We use the term *variables* to include those factors or aspects of experience addressed in both qualitative and quantitative observational and intervention studies. We will use this list of variables to address Aims 1 and 3. We will map the relationships found in qualitative and quantitative observational studies among condition management and control; the functioning of affected child, parents, and siblings; family life and functioning; family relationship with the healthcare system; and individual and family demographics; in addition to the relationships found in intervention studies between interventions and outcomes. This mapping will be the basis for addressing Aims 2 and 4. Table 2 is a provisional, heuristic categorization to guide sample selection and development of templates for conducting the review of articles. We anticipate that in the course of mapping these relationships, we will modify this variable list to accommodate the findings in the reports of the studies reviewed. Table 2 specifies a list of variables, not their relationships to each other as any one of these variables may have been studied as independent, intervening, and/or dependent variable.**

The sample will include all relevant reports of empirical research published in English between 1995 and the present (with relevant updates until 2014) that contain findings addressing the intersection between family life and childhood CPCs. We use the word *intersection* here to signal the various and dynamic ways these concepts will have been empirically related in the research reports included. The year 1995 was chosen to ensure a timely review [79-80] that is relevant to contemporary family structures and understandings and treatments of childhood CPCs. Reports of studies with timely findings conducted prior to 1995, however, may be included as warranted by ongoing analyses. *Empirical research* is defined as any qualitative, quantitative,

experimental, or mixed-methods study addressing any meeting points between and among the concepts targeted in the research questions.

Current definitions of *childhood chronic condition* focus on duration and impact of the condition on the child rather than delimiting specific diagnoses [81-83]. Accordingly, we are defining a *childhood chronic physical condition* as lasting or expected to last at least one year and producing or expected to produce one or more of the following sequelae for the child: limitation in function/activity, dependency on medication, special diet, medical technology, assistive devices or personal assistance, and/or need for medical care or related services beyond what is usual for a child of the same age [82]. *Child* is defined as an individual less than 18 years of age. We will limit our search to empirical studies of childhood CPCs where normal development occurs in the context of the condition.

**Table 2. Initial Categorization of Study Variables**

**Condition management & control**

Condition status (e.g., glycemic level, respiratory volume)  
 Condition trajectory (e.g., stable, relapsing, symptom profile)  
 Condition/treatment knowledge  
 Condition/treatment beliefs  
 Symptom management  
 Regimen management (e.g., medication, diet, activity)  
 Caregiving management  
 Self-management  
 Use of CAM

**Parent (mother/father) functioning & experience**

Health (e.g., eating, sleeping)  
 QOL, wellbeing, satisfaction, hope  
 Self-efficacy, mastery, locus of control, adaptive style  
 Work performance  
 Parental performance (parenting style, competence)  
 Psychosocial (e.g., depression, anxiety, stress/strain, PTSS/PTSD, self-image, coping)  
 Perceptions (e.g., condition, child, family life)

**Family life & functioning**

Family (mother/father/sibling/affected child) relations, interactions  
 Family schedules, routines, rituals  
 Member communication  
 Management styles, Division of labor (e.g., teamwork)  
 Family intimacy, cohesion, conflict  
 Adjustment/adaptation trajectories  
 Social support (e.g., emotional, instrumental)  
 Stigma & discrimination  
 Appraisal & coping  
 Quality of family life/functioning  
 Family environment  
 Perceptions (e.g., of family/other members, condition impact)  
 Congruence across family members

**Affected child functioning & experience**

General health (e.g., sleeping, eating, mobility)  
 QOL, wellbeing  
 School performance  
 Peer interactions  
 Psychosocial (e.g., depression, anxiety, self-image, coping)  
 Behavior  
 Perceptions (e.g., condition, everyday life)

**Sibling functioning & experience**

General health (e.g., sleeping, eating, mobility)  
 QOL, wellbeing  
 School performance  
 Psychosocial (e.g., depression, anxiety, coping)  
 Behavior  
 Perceptions (e.g., condition, everyday life)

**Healthcare system**

Health and social services utilization  
 Healthcare costs  
 Needs/satisfaction  
 Family/professional provider relations

**Demographics (individual & family)**

Age/developmental stage,  
 Sex  
 Race/ethnicity  
 Class  
 Education  
 Other background characteristics (e.g., maternal reproductive history, family history of condition)  
 Family structure (e.g., single-parent, blended)  
 Location (urban, rural)

In contrast to children with serious developmental, behavioral, and psychiatric conditions, children with CPCs typically are schooled in regular classrooms and engage in usual (though possibly limited) childhood activities and peer relationships. At the same time, they and their families must adapt their daily lives to the demands and limitations imposed by the condition. Prior research has addressed child/family responses to CPCs as a unique area of inquiry [2-4, 28]. Psychiatric, developmental, or behavioral conditions are typically viewed as other subsets of all chronic conditions [81] and will therefore not be included. **Although we will exclude reports of studies in which the primary diagnosis is psychiatric or behavioral, we will extract data on the psychological and behavioral functioning of children from the reports included in the proposed study. Data will be extracted on co-morbid conditions as well.** Also excluded will be reports of studies

focused on end-of-life issues, which is itself the subject of a large and distinctive body of research. The focus of the proposed study is on the daily life of families **from diagnosis throughout the course of condition management**.

Because childhood CPCs are managed across a broad array of family contexts, *family* is defined to capture this diversity [84]. *Family* is a group of intimates living together or in close geographic proximity with strong emotional bonds and with a history and a future [85]. The term *family* includes the family system, sub-systems, and individuals fulfilling family roles (e.g., child, parent, sibling). We will include reports of studies that address family member, system, and subsystem management of the condition, outcomes of the condition, and factors influencing condition management and outcomes. Reports will be included that are focused either on family and family life, or on key family members (e.g., mothers, fathers, affected child, siblings) alone or in relation to other family members, in the context of CPCs. Reports will be included regardless of how a concept, such as family cohesiveness, is studied (e.g., as risk/ protective factor, response, consequence) and of whether the data collected were from, for example, mothers about themselves, or from fathers or providers about mothers. This inclusion will allow study of the link between sources of information (vantage points) and the information itself. Our search will build on work completed in our preliminary studies, with data bases and search terms revised as warranted. Other possible sources of reports will include relevant published books and anthologies available in the University of North Carolina at Chapel Hill library system. Ancestry and descendency approaches to searching [86] from reports accepted as relevant will be used. **As there is already a massive volume of information available from published sources, to optimize the feasibility of the proposed study, we will search for unpublished materials (e.g., theses, dissertations) as warranted (e.g., instances of insufficient or conflicting information). As a further check, we will review dissertations completed between 1995 and the present to determine if there is any factor with regard to the variables, conditions, or target populations being studied that would warrant their inclusion. Our initial screen of dissertations published between 2000 and 2005 indicates that this is not the case and that 24% of them resulted in published reports that will be captured in our searches.**

#### **Data Collection (Extraction of Information from Reports)**

As soon as reports are retrieved, basic information will be extracted from each one, as shown in the data extraction guides in Appendix A, and placed in databases that will eventually include all the reports that will contribute to the proposed study. Data matrices will then be generated from these databases specific to each research **aim**. Effects sizes of all relevant findings from quantitative observational and experimental studies will be calculated (using CMA software); thematic statements or models (e.g., in the case of findings in the form of grounded theories) will be constructed to represent all relevant findings from qualitative studies [87].

Each report will also be appraised for its timeliness and general signal-to-noise ratio (i.e., balance between informational value and methodological shortcomings [88]). Yet, no findings will be excluded a priori for reasons of quality. Quality appraisals have recurrently been shown to be highly idiosyncratic enterprises that lead to losses of valuable information not invalidated by methodological deficits (e.g., [86-87]). In the proposed study, the signal-to-noise ratio of reports will be used in sensitivity analyses, for example, to determine whether the source of a set of findings is largely from high “noise”/low “signal” studies where methodological flaws outweigh informational value, or low “noise”/high “signal” studies where informational value outweighs methodological flaws.

#### **Data Analysis**

The findings extracted from each study will then be grouped to capture their diverse topical foci; one finding may, therefore, be placed in more than one group. For example, regardless of its methodological pedigree (i.e., qualitative, quantitative observational, experimental, mixed-methods study), a finding indicating that mothers’ depression had a negative influence on the affected child’s adherence to a specific diet will be grouped with other findings focused on (a) maternal mood, (b) affected child adherence to prescribed health regimens, and (c) dietary regimens. A finding indicating that an equal family division of labor in the care of the affected child contributed to beneficial family and child functioning will be grouped with other findings focused on the (a) the work of condition management, (b) family functioning, and (c) child functioning. To begin, findings in common topical domains will be grouped together regardless of their thematic relationship (e.g., confirming, refuting). For example, findings indicating that mothers’ depression had a negative influence on the affected child’s adherence to a specific diet will initially be grouped with findings indicating that mothers’ depression had a positive or no influence on the affected child’s adherence to a specific diet.

Data matrices will be created aligning each finding in every topical group with methodological features



important to how they should be interpreted or can be synthesized (e.g., whether linked to numbers and characteristics of participants, whether produced from self- or other-report, whether produced from open- or closed-ended data collection). For example, as noted previously, a set of thematically similar findings may permit pooling at the study level but not at the subject level because their origin is primarily from qualitative studies with limited or no information available on the numbers of participants linked to findings [74, 76]. Topical grouping of findings will allow us to see the diversity, range, and emphasis in, and thematic relationships among findings, while preserving their varied individual contexts. Within-topical group thematic analyses also avoid the persistent problem of assuming differences between “qualitative” and “quantitative” studies that are not relevant to the actual studies included in a review. One such assumed difference is that qualitative findings offer more penetrating and nuanced understandings of singular actors, events, and processes than quantitative findings. Yet, qualitative surveys do not meet this criterion. Because they resemble—in their minimal degree of interpretation—quantitative surveys more than they resemble other highly-interpretive qualitative findings (e.g., grounded theories or phenomenological descriptions [87], these findings are actually more amenable initially to aggregation (pooling) with other quantitative survey findings than they are to configuration with more interpretive qualitative findings. Thematic analysis within topical groupings at a beginning stage of a mixed research synthesis project avoids the default segregation of findings until the final stage of a project solely on the basis of stated method, thereby allowing all findings to contribute to all stages of the analysis process.

### Data Synthesis

After the thematic analysis of findings within all of the topical groups is completed, findings will be organized for synthesis by the research aims. Bayesian meta-analysis will be used to aggregate thematically similar findings and a realist synthesis approach will be used to configure thematically disparate sets of pooled and individual findings. **As detailed below, these approaches used in combination are especially amenable—by virtue of their flexibility and inclusiveness—to meeting the key challenges of research synthesis studies, including managing methodologically diverse and missing data, and small sample sizes.** Multiple research syntheses—in the form of evidence summaries and theoretical integrations of research findings—will be produced that can serve as foundations for programs of care for and intervention research with families.

Bayesian meta-analysis. Meta-analysis is the combination of results from multiple primary studies [89]. Traditional meta-analysis has been focused on mathematical pooling of estimates from methodologically similar studies, with the field developing to include more dissimilarity. Mixed research synthesis poses a challenge to traditional meta-analysis, as it requires the combination of findings from vastly different study designs, and from qualitative and quantitative studies. As described in **three** papers published by members of the research team of the proposed study [76-77, 90] (copy of #76 & #90 in Appendix B), **Bayesian approaches have two major advantages for mixed research synthesis. First, they allow for the combination of information that resists direct mathematical combination or pooling by creating statistical distributions representing each of the pieces of information and then combining them. Second, Bayesian methods are adept at dealing with missing data [20],** the norm in any research synthesis project as studies within a domain of research will differ widely with respect to the variables targeted for examination. Rather than excluding studies that do not address certain relationships or themes, or restricting analysis to a very small number of them, Bayesian data augmentation (latent variable) models can be used to include all studies that address at least one of them. **The results of Bayesian meta-analysis are dependent on the choice of prior distribution; we will therefore assess the robustness of every result through sensitivity analyses varying the prior distribution [73]. A result that varies widely based on the choice of prior distribution is not reliable and will therefore not be reported. In this case, the flexibility of the Bayesian approach makes it ideal for adaptation by synthesizing data with a variation of the original method or with the extracted data in a different form until a reliable result is obtained.** Bayesian analyses will be conducted using WinBUGS and Matlab.

Illustration of Bayesian approach. Although we will use traditional Bayesian meta-analysis for synthesis of data from quantitative studies, we demonstrate here the utility of Bayesian methods for the synthesis of quantitative and qualitative data. Table 2 illustrates different types of information available in a set of fictitious qualitative and quantitative studies linking aspects targeted in **Aims 1, 3, and 4.**

Reports A, B, and C show quantitative results, represented by effect sizes. In Studies A and B, researchers measured the impact of a family **problem-solving** intervention on **family conflict** in families with children with CPCs. Study C is a quantitative descriptive study of quality of life in families whose children were diagnosed

with diabetes 5-8 years previously. Study D is a qualitative description of family life with children **with a CPC focused on perceptions of problem-solving based on participation in a program offered through the local children's hospital**, and Study E is a qualitative description of mothers **whose children are adults** reflecting on the impact of raising a child with a CPC **on their families**. The results from these qualitative and quantitative studies cannot be directly pooled. But, depending on the information available in the qualitative studies, the qualitative study findings could be converted to plausible ranges of effect sizes, as described in Chang et al. [74], and combined with the effect sizes from the quantitative studies to obtain a pooled estimate, as described in Voils et al. [77].

**Table 2. Example of Data Matrix for Bayesian Meta-analysis**

Study	Study N (number of families)	Example for Aim 1: Does a higher caregiving demand lead to more marital conflict?	Example for Aim 3: Does a family problem-solving intervention decrease family conflict?	Example for Aim 4: Is the effectiveness of the problem-solving intervention related to family structure?
A (intervention study)	54	n/a	.33	.23
B (intervention study)	101	n/a	.19	.04
C (quantitative descriptive)	62	.06	n/a	.36
D (qualitative descriptive)	15	5-10	3-8	2-6
E (qualitative descriptive)	35	10-25	n/a	n/a

Note. Example effect sizes are given for the quantitative studies, and plausible sample size ranges for the qualitative studies; *n/a* denotes a question that was not addressed in a report.

Or, as described in Crandell et al. [76], the presence or absence of a relationship or theme from both the qualitative and quantitative results could be coded as 0 or 1 and a Bayesian method (with provisions for missing data) used to estimate the prevalence of a certain conclusion across reports. Alternatively, Roberts et al. [91] proposed a method not for direct pooling, but rather for using the qualitative results to inform the priors for synthesis of the quantitative results. This method does not involve direct pooling of qualitative and quantitative findings, but still allows both to be included in the synthesis.

**Realist synthesis.** As Pawson [18] described it, realist synthesis is focused on reviewing empirical research findings with the goal of accumulating explanations for the effects that differences in processes (e. g., management strategies) and contexts (e.g., family systems) have on outcomes. **Whereas Bayesian synthesis yields summative statements on relationships among variables, realist synthesis yields explanations for how they are related.** Realist synthesis also emphasizes collaboration with key decision-makers concerning the analytic focus of research syntheses. Realist synthesis begins with a preliminary explanatory model and then proceeds to locating evidence from targeted reviews of the literature conducted to address each component of that model. Literature searching in realist synthesis studies is an iterative process as the evidence yield from any one search will lead to other targeted searches. The end-products of realist synthesis studies are theories that have been successively refined to accommodate the evidence retrieved. The preliminary explanatory model can be drawn from existing theories or frameworks (top-down, as from one or more grounded theories constituting a set of qualitative findings), or derived from an initial scoping review of the literature or from thematically disparate sets of pooled findings (bottom-up). Members of the research team used realist synthesis to model steps critical to implementing an antiretroviral adherence intervention and variations in those steps across different intervention processes and contexts [92].

**Illustration of realist synthesis approach.** Figure 2 illustrates a preliminary explanatory model that could be derived from initial analysis of research findings in response to **Aim 1 (Map the relationships found among condition management/control; the functioning of affected child parents, and siblings; family life and functioning; family relationships with the healthcare system; and family demographics)** and **Aim 2 (Explain how these factors operate together to produce variations in child and family outcomes)**. Figure 2 addresses only one component of possible responses to these aims; additional models would be developed

to address other components. We will create a model such as that depicted in Figure 2 if an initial analysis of multiple findings suggesting that specific characteristics of primary caregivers, family functioning, **and the family's relationship with the healthcare system interact to influence condition management and outcomes.** We would then use this preliminary model as a guide to further mine and analyze data to evaluate the relative importance of the identified factors as children develop, thereby configuring data from cross-sectional studies to assess the varying effects of contextual factors across developmental stages. Based on those findings, we would then further refine the model to specify the importance of each of the factors and their relationship to each other over the course of children's development. As the analysis progressed, we might identify a subset of data that does not fit the emerging pattern, such as children with a particular type of condition, and would further refine the theory to accommodate this new information.

**Figure 2. Preliminary Explanatory Model in Response to Aims 1 & 2**

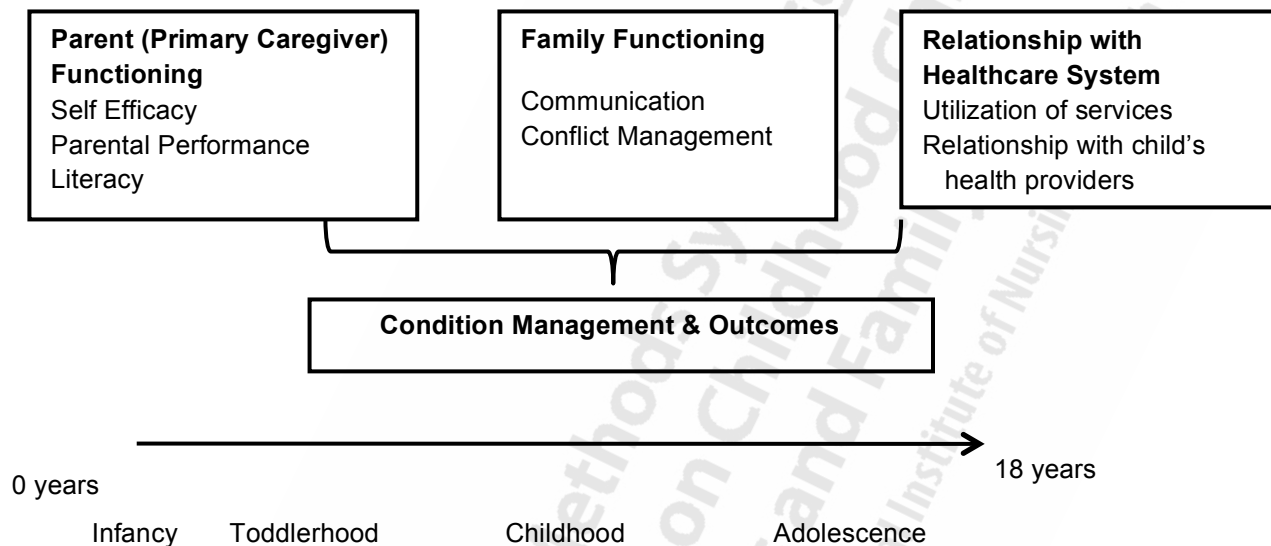
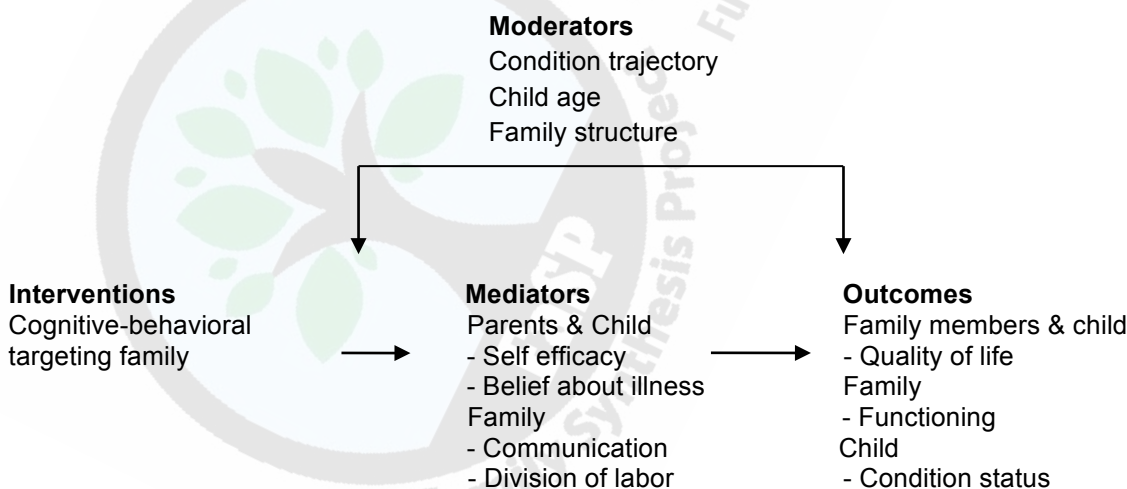


Figure 3 illustrates how data analyzed in response to **Aim 3 (Describe the nature of interventions directed to families of children with CPCs and their effects on child and family outcomes)** and **Aim 4 (Examine factors moderating and mediating intervention effects)** could be used to configure a preliminary explanatory model in response to Aim 4. Data analyzed in response to Aims 3 and 4 may show that most interventions used with families of chronically ill children can be categorized as cognitive behavioral and that the theories underlying these interventions posit a range of mediators to explain how interventions affect outcomes.

**Figure 3. Preliminary Explanatory Model in Response to Aims 3 & 4**



Data will show the **effects of interventions on both the outcomes of childhood conditions and on potential mediators of intervention effects.** Patterns in the findings across studies further suggest that

characteristics of **the condition trajectory**, family structure, and child's developmental stage, may moderate the effects of cognitive-behavioral interventions. The explanatory model would then be used to guide further data mining and analysis to assess the strength of the proposed relationships, further augmenting and refining theory. **Such an analytic process allows the testing of** relationships not tested in the original studies. For example, full analyses of mediation effects can be done by combining findings across studies that themselves provide only part of the findings needed to test mediation [93].

### **Procedures to Optimize Validity of Research Syntheses Produced**

We view validity as encompassing two key components: scientific credibility and utilization value.

Scientific credibility. Procedures to optimize the scientific credibility of the research syntheses produced will include having an information specialist (Shaw-Kolkot) as co-I to optimize targeted search strategies; tracking and organizing all search results via reference manager software and Microsoft Access databases; contacting authors of primary studies to obtain additional information as needed; convening weekly meetings of the research team to discuss ongoing progress and address specific issues arising in each phase of the study; having at least two members of the research team independently extract, calculate, and transform all data, with areas of disagreement addressed in weekly research team meetings; and research consultation with family researchers and clinical decision makers as needed throughout the project. In addition, various post hoc analyses will be conducted to assess how characteristics of the studies (e.g. disciplinary affiliation, publication venue, national/geographic location, theoretical framing, mode of data collection, overall quality, sample composition) contributed to the results of the syntheses produced.

Utilization value. The purpose of this study is to advance both research and practice with the ultimate goal of improving care for families with children with CPCs. Assessing the utility of review findings for researchers will be a primary function of the team's research consultants. The greater challenge will be to ensure that findings contribute to clinical care and also to the advancement of more clinically relevant research.

**To optimize the utilization value of the research syntheses produced we will collaborate with clinical decision makers (clinicians providing direct care or engaged in program development, managers of care delivery) beginning in Year 1 and throughout the project.** To improve practice, research findings must reach and influence clinical decision makers who have recurrently reported that the findings from systematic reviews too often are not accessible, usable, or relevant to their practice [94-96]. Therefore, soliciting their input is critical to increasing the utility, relevance and accessibility of findings and thereby their impact on practice [97-98]. Soliciting input will ensure that the research team is focusing on priorities and problems of clinical importance [99], identifying key messages that communicate findings to clinical decision makers [100], and selecting formats and strategies that effectively disseminate findings [97, 101-102].

**Accordingly, we are soliciting input from clinical decision makers representing nursing and other key disciplines providing care to families with children with CPCs (e.g., medicine, clinical psychology). We have created an Advisory Committee of clinical decision makers who were purposefully selected to include individuals with at least ten years of clinical experience caring for children with chronic conditions and their families and who represent diverse disciplines, practice settings, and geographic locations (see letters of support). We chose individuals who either had experience with children with a broad range of chronic conditions or with one of the more prevalent conditions (cancer, diabetes, or asthma). We plan to solicit the Advisory Board's input through convened meetings and individual consultation beginning in Year 1 of the project. We also will do usability testing of targeted evidence summaries with 10-15 additional clinicians who will be purposely selected based on input from Advisory Committee members.**

***Clinical Decision Maker Advisory Committee meetings.* We will hold three extended (3-4 hours) teleconferenced meetings with our Advisory Committee to solicit their input as we focus our analyses, identify practice-relevant key messages, and develop dissemination formats and strategies [99, 103]. At the first meeting in Year 1 of the grant, we will ask for feedback on our research aims, modes of searching, and results of initial analyses of reports. Committee members will have received materials to review prior to the meeting. At the second meeting in Year 3, we will present the evidence summaries and explanatory models completed to date, which Advisory Committee members will also have received prior to the meeting with a list of questions to consider. We will ask members to provide feedback about the materials they received and to discuss the clinical utility and scope of review findings (e.g., whether there are key factors that affect family management of chronic conditions that**

remain unexplored). The goal of these meetings is to further focus the review towards clinically relevant questions and priorities. At the third meeting, toward the end of Year 4, we will present the near-final evidence summaries and theoretical integrations and ask members to help us distill the findings that are most relevant and important for practitioners and suggest ways to frame those key messages for them [100]. We will confer individually with Committee members every year of the study.

**Developing and usability testing dissemination formats.** Based on input from our Clinical Decision Maker Advisory Committee and professional organization partners (see Dissemination Plan), in Year 5 we will develop evidence reports targeted to clinicians that highlight key practice-relevant findings. The evidence reports will include both summaries and theoretical renderings of evidence. UNC’s NIH-funded Communication for Health Applications and Interventions (CHAI) Core will work with us to create and test visually appealing and user-friendly reports for dissemination in both print and electronic formats. We then will conduct cognitive response interviews and usability-tests of the reports with 15 clinical decision makers who will be identified in consultation with the Clinical Decision Maker Advisory Committee and our professional organization partners. CHAI staff have extensive experience using both methods [104-105]. We anticipate creating up to three evidence reports and testing each with five clinical decision makers knowledgeable in the areas targeted. A member of the CHAI core with expertise in cognitive response interviewing and usability assessments will then interview the clinician, using an interview guide to assess understanding of content, readability, and clinical relevance and to solicit suggestions for improvement. These interviews will be audio-recorded and transcribed for analysis. We will further refine the evidence reports based on results of the usability tests and input from organizational partners. Our ultimate goal is to achieve broad dissemination using a range of formats and strategies.

**Dissemination plan.** The study team will publish and present its findings in both research and professional venues. To ensure that findings reach a broad clinical audience, we will partner with professional organizations representing clinicians who care for families of children with CPCs to disseminate the evidence reports in a format and outlet that is appropriate for their members (see letters of support from the Association of Pediatric Endocrinology Nursing Society, International Family Nursing Association, International Society of Nurses in Genetics, National Association of Pediatric Nurse Practitioners, National Association of School Nurses, Pediatric Endocrinology Nursing Society, and Society of Pediatric Nursing). We will work with these organizations to identify a range of dissemination formats tailored to provide relevant information to members (e.g., the organization’s newsletter and website, interactive web-based CE programs). We anticipate identifying other organizations with whom to partner for effective dissemination during the course of the study. We will ask our Clinical Decision Maker Advisory Committee for additional suggestions of strategies to disseminate findings broadly (e.g., clinical journals, newsletters and listservs, conferences).

**End-Products of Proposed Study**

The end-products of the proposed study will be: (a) evidence summaries addressing each of the research aims; (b) “theories” of the problem (i.e., theoretical integrations describing or explaining the different challenges families with children with CPCs face that are amenable to intervention); and (c) “theories” of the intervention (i.e., theoretical integrations serving as foundations for actions targeting one or more of these problems). These will be disseminated in forms accessible to and usable by researchers conducting family research and intervention testing and clinical decision makers creating programs of care for these families.

**Timeline**

The timeline for the proposed project is shown below.

ACTIVITIES/YEAR BEGINNING	07/1/11	07/01/12	07/01/13	07/01/14	07/01/15
Project start-up	---				
Search & retrieval of research reports	-----	-----	-----	-----	
Data Extraction	-----	-----	-----	-----	
Data analysis (grouping of reports by topical focus & thematic analysis)	-----	-----	-----	-----	
Data synthesis (synthesis to address research aims 1-4)		-----	-----	-----	
Writing evidence syntheses			-----	-----	-----

Research Consultation	-----	-----	-----	-----	-----
Clinical Consultation	-----	-----	-----	-----	-----
Usability tests with clinical decision makers					-----
Dissemination of results		-----	-----	-----	-----



*Mixed Methods Synthesis of  
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Conditions and Family*

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