STUDY PROTOCOL WITH STATISTICAL ANALYSIS PLAN AND INFORMED CONSENT FORM

Factors Associated with Insulin Pump-Related Skin Complications in Children with Type 1 Diabetes: A Cross-sectional Study

Protocol version	Draft English version 1.0; prepared from the Chinese investigator-initiated study application
Protocol date	30 April 2026
ClinicalTrials.gov NCT number	To be assigned
Sponsor/Institution	Children's Hospital, Zhejiang University School of Medicine
Principal Investigator	Xiaochun Chen
Department	Department of Endocrinology
IRB approval number	2025-IRB-0077-P-01
Study design	Observational, cross-sectional study
Study setting	Three tertiary children's hospitals in Zhejiang Province, China; confirm final registration field if submitted as single-center
Planned sample size	199 child-caregiver pairs; confirm if the final approved number is 100 or 199
Planned study period	July 2026 to June 2027 for enrollment and data collection; confirm if local documents require January 2026 to December 2026

Important pre-submission note: Several items in the Chinese source application require confirmation before ClinicalTrials.gov submission: single-center vs three-center design; total sample size 100 vs 199; and conflicting study dates. This English draft uses the internally consistent methods description of three hospitals, 199 participants, and July 2026 to June 2027 enrollment, and flags these points where relevant.

1. Protocol Synopsis

Official title	Factors Associated with Insulin Pump-Related Skin Complications in Children with Type 1 Diabetes: A Cross-sectional Study
Brief title	Skin Complications in Children With T1D Using Insulin Pumps
Condition	Type 1 diabetes mellitus; insulin pump-related skin complications
Study type	Observational
Observational model	Cross-sectional assessment of children with T1D and their primary family caregivers
Time perspective	Cross-sectional
Allocation / intervention	Not applicable; no randomization and no intervention
Primary objective	To estimate the prevalence of insulin pump-related skin complications in children with type 1 diabetes and identify associated factors, including subcutaneous fat thickness, skin characteristics, pump-use behaviors, and caregiver knowledge, attitudes, and practices.
Secondary objectives	To describe caregiver knowledge, attitudes, and practices; examine associations with quality of life; evaluate whether catheter type/specification and insertion practices are compatible with skin and subcutaneous fat thickness; and describe caregiver responses after complications occur.
Primary outcome	Presence of any insulin pump-related skin complication, assessed by standardized skin evaluation and recorded as yes/no.
Secondary outcomes	Complication type and severity; anatomical-site-specific skin/subcutaneous fat thickness; site-specific complication rates; caregiver KAP score; quality-of-life score; pump-use and infusion-set factors.
Population	Children diagnosed with T1D who have used insulin pump therapy for at least 6 months, and their primary family caregivers.
Sample size	199 child-caregiver pairs, based on expected prevalence of 66.8% and formula N = 400Q/P.

2. Background and Rationale

Type 1 diabetes mellitus (T1D) is a chronic disease that substantially affects child health and requires lifelong insulin replacement therapy. Insulin replacement can be delivered by multiple daily injections or continuous subcutaneous insulin infusion (CSII). CSII is an important insulin delivery method for children with T1D because it can mimic basal insulin secretion and provide flexible mealtime bolus dosing.

Despite the benefits of CSII, skin-related complications are common and can negatively affect comfort, device adherence, glycemic control, and quality of life. Insulin pump-related skin complications include lipohypertrophy, lipoatrophy, scarring, local erythema, subcutaneous infection, irritant contact dermatitis, and allergic contact dermatitis. Children may be particularly vulnerable because of limited subcutaneous fat, fragile skin, and a limited number of feasible infusion sites.

Previous studies have used variable definitions and assessment methods for insulin injection- or pump-related skin complications. Reported associated factors include sex, duration of T1D, caregiver educational level, allergic skin

tendency, and concomitant use of continuous glucose monitoring devices. However, the actual prevalence, lesion characteristics, and contribution of children's skin and subcutaneous fat thickness remain insufficiently understood in Chinese pediatric populations. Caregiver knowledge, attitudes, and practices related to skin care may also influence risk and management.

This study will use structured questionnaires, standardized skin assessment, and objective measurement of skin/subcutaneous fat thickness to identify risk factors and provide evidence for individualized skin-protection education and management strategies for children with T1D using insulin pump therapy.

3. Objectives and Hypotheses

3.1 Primary Objective

To investigate the prevalence of insulin pump-related skin complications among children with T1D and explore associated factors, particularly skin/subcutaneous fat thickness at the arms, abdomen, buttocks, and thighs, skin type, and insulin pump-use behaviors.

3.2 Secondary Objectives

1. To assess primary family caregivers' knowledge, attitudes, and practices regarding insulin pump-related skin complications.
2. To evaluate whether infusion-site skin complications are associated with children's quality of life.
3. To examine whether catheter type, catheter specification, and insertion methods are appropriate for children's measured skin and subcutaneous fat thickness.
4. To describe whether caregiver management measures after skin complications occur are appropriate.

3.3 Hypotheses

- H1: The prevalence of insulin pump-related skin complications in children with T1D is significantly associated with subcutaneous fat thickness, skin type, and pump-use behaviors.
- H2: Higher caregiver knowledge-attitude-practice scores are associated with lower risk of skin complications in children.
- H3: A prediction model incorporating skin/subcutaneous fat thickness, caregiver KAP factors, pump-use behaviors, and skin complications can provide quantitative evidence for future individualized prevention strategies.

4. Study Design

This is an observational, cross-sectional study. No randomization, allocation, investigational product, or experimental intervention will be used. Eligible children with T1D who have used insulin pump therapy for at least 6 months and their primary family caregivers will be recruited consecutively from participating pediatric endocrinology departments.

Data collection will include structured questionnaires, skin assessment, photographic documentation when appropriate, and objective measurement of skin/subcutaneous fat thickness using a wireless handheld ultrasound device and skinfold calipers. The Chinese source document contains both "single-center" and "three tertiary children's hospitals" descriptions; the final registration should match the IRB-approved protocol.

5. Study Population

5.1 Inclusion Criteria for Children

5. Diagnosed with T1D according to WHO-recommended diagnostic criteria or applicable national guidelines.
6. Duration since T1D diagnosis of at least 6 months.
7. Current insulin delivery primarily by insulin pump therapy.
8. No cognitive or consciousness disorder that would prevent cooperation; able to read or cooperate with age-appropriate instructions.
9. The child and/or legal guardian agrees to participate, as applicable.

5.2 Inclusion Criteria for Primary Family Caregivers

10. Able to understand study information and complete the questionnaire.
11. Voluntarily agrees to participate.
12. Provides an average of at least 6 hours of daily care for the child.

5.3 Exclusion Criteria

13. Children with acute or chronic diabetic complications requiring urgent treatment or preventing cooperation.
14. Children in a disease stress state such as acute infection, surgery, or trauma.
15. Caregivers with unconsciousness, psychiatric abnormality, hearing or language impairment preventing valid participation, or duplicate survey participation.

5.4 Withdrawal and Discontinuation

Participation is voluntary. A legal guardian or child may withdraw at any time without giving a reason and without affecting current or future medical care. The investigator may discontinue procedures if urgent treatment is required, if continued participation is not in the participant's best interest, or if required by the ethics committee or regulatory authority.

6. Recruitment and Consent Procedures

Potentially eligible children and caregivers will be identified by trained research staff in pediatric endocrinology settings. The investigator will explain the purpose, procedures, possible risks, benefits, confidentiality protections, and voluntary nature of the study in understandable language. Written informed consent will be obtained from the child's legal guardian and from the caregiver participant. Child assent will be obtained when appropriate according to the child's age, literacy, and local ethics requirements.

7. Study Procedures

7.1 Questionnaire Assessment

Trained investigators will distribute structured questionnaires using standardized instructions. Questionnaires will collect demographic and clinical information, pump-use behaviors, caregiver knowledge, attitudes, and practices regarding skin complications, and quality-of-life information where applicable. Investigators will check questionnaires when returned to reduce missing or incorrect items.

7.2 Skin and Subcutaneous Fat Thickness Measurement

Qualified personnel with ultrasound training will measure skin and subcutaneous fat thickness at standardized anatomical sites, including the arms, abdomen, buttocks, and thighs. Measurements will be performed using a wireless handheld ultrasound device and skinfold calipers according to a unified measurement manual. Images or records will be retained using participant study codes. Two trained assessors will review ultrasound measurements.

7.3 Skin Complication Assessment

Skin complications will be assessed using standardized criteria. Complication type may include lipohypertrophy, lipoatrophy, pigmentation change, scarring, erythema, pain, fear/avoidance related to infusion-site use, infection, irritant dermatitis, or allergic contact dermatitis. Where permitted by consent, lesions may be photographed for documentation and adjudication. A dermatologist or trained skin specialist will review photographs and/or clinical findings to determine the final classification and severity.

7.4 Follow-up

This is a cross-sectional study and does not require protocol-defined follow-up. If clinically relevant skin abnormalities are identified, participants will receive appropriate advice or referral according to usual clinical practice.

8. Outcome Measures

8.1 Primary Outcome Measure

The primary outcome is the presence of any insulin pump-related skin complication at the time of assessment, coded as yes/no. The numerator will be the number of children with at least one pump-related skin complication, and the denominator will be the total number of evaluable children.

8.2 Secondary Outcome Measures

- Prevalence of each specific skin complication type.
- Severity of skin complications, if categorized in the standardized assessment form.
- Skin and subcutaneous fat thickness at arms, abdomen, buttocks, and thighs.
- Differences in complication rates by anatomical site.
- Caregiver knowledge-attitude-practice total and subscale scores.
- Quality-of-life scores and their association with skin complications.
- Catheter type, catheter length/specification, insertion method, site rotation, infusion-set replacement interval, disinfection practices, and related pump-use behaviors.

9. Sample Size

The planned sample size is 199 child-caregiver pairs. The calculation is based on $N = 400Q/P$, where P is the expected prevalence and $Q = 1 - P$. Using an expected prevalence of 66.8% from prior work by the study team, the required sample size is approximately 198.8, rounded to 199. The final registration should confirm whether the IRB-approved sample size is 199 or 100, because the source Chinese document contains both values.

10. Statistical Analysis Plan

10.1 Analysis Populations

The full analysis set will include all enrolled participants with valid primary outcome data. Participants with missing primary outcome data will be excluded from the primary prevalence analysis but included in descriptive analyses where relevant data are available.

10.2 General Statistical Principles

Analyses will be conducted using SPSS version 22.0 or a later validated statistical software package. Statistical tests will be two-sided. A P value <0.05 will be considered statistically significant. Estimates will be reported with 95%

confidence intervals where appropriate. The analysis will primarily be exploratory and hypothesis-generating because the study is cross-sectional.

10.3 Descriptive Analysis

Normally distributed continuous variables will be summarized as mean and standard deviation. Non-normally distributed continuous variables will be summarized as median and interquartile range. Categorical variables will be summarized as frequencies and percentages. Caregiver KAP scores will be summarized as mean and standard deviation, or median and interquartile range if distributional assumptions are not met.

10.4 Primary Outcome Analysis

The prevalence of any insulin pump-related skin complication will be calculated as the number and percentage of children with at least one complication among all evaluable children. A 95% confidence interval will be reported. Site-specific prevalence will be calculated for abdomen, buttocks, arms, and thighs when anatomical-site data are available.

10.5 Univariate Analysis

Potential associated factors will be assessed using univariate analyses. For categorical variables, chi-square tests or Fisher's exact tests will be used as appropriate. For continuous variables, independent-samples t tests, one-way analysis of variance, Mann-Whitney U tests, or Kruskal-Wallis tests will be used according to distributional characteristics and group numbers. Candidate variables may include age, sex, duration of T1D, duration of pump therapy, BMI or nutritional status, allergic skin tendency, concurrent CGM use, infusion-site rotation, infusion-set replacement interval, disinfection practices, catheter type and specification, anatomical-site thickness, and caregiver KAP scores.

10.6 Multivariable Logistic Regression

Multivariable logistic regression will be used to identify independent factors associated with any skin complication. Variables with clinical relevance and/or $P < 0.10$ in univariate analysis may be considered for model entry, while avoiding overfitting relative to the number of outcome events. Adjusted odds ratios, 95% confidence intervals, and P values will be reported. Model fit and discrimination may be assessed using the Hosmer-Lemeshow test and area under the receiver operating characteristic curve, if appropriate.

10.7 Prediction Model Analysis

If data quality and event numbers are adequate, an exploratory prediction model incorporating skin/subcutaneous fat thickness, caregiver KAP scores, and pump-use behaviors will be developed for risk of skin complications. Internal performance may be evaluated using discrimination, calibration, and, if feasible, bootstrap or split-sample internal validation. External validation will be required before clinical use.

10.8 Missing Data

The extent and pattern of missing data will be described. For questionnaire items, scoring rules of the corresponding instrument will be followed. If missing data are limited, complete-case analyses will be used. If missingness is substantial and plausibly missing at random, sensitivity analyses using appropriate imputation methods may be considered.

10.9 Data Presentation

Results will be presented in tables and figures, including participant flow, baseline characteristics, prevalence of complications, site-specific measurements, univariate comparisons, and multivariable regression results. No interim analysis is planned.

11. Data Management and Quality Control

Questionnaire data will be entered electronically with logic checks when possible. Skin thickness and ultrasound measurement data will be entered using double data entry. Discrepancies greater than the predefined threshold, such as more than 1 mm for thickness measurements, will be reviewed and corrected based on source records. Participants will be assigned anonymous study codes such as T1D-001. The study database will be stored in encrypted local storage with secure backup. Access will be limited to authorized study staff.

Research staff will receive standardized training before data collection. Periodic checks will identify missing data, logical errors, and protocol deviations. A random sample of questionnaires or records may be verified by telephone or source review. A data and safety monitoring/quality group may review privacy protection, data consistency, and safety findings at regular intervals.

12. Safety Considerations and Risk Management

This study involves questionnaires, skin inspection, non-invasive ultrasound measurement, and skinfold caliper measurement. No study drug or invasive intervention will be administered. The main potential risks are mild skin discomfort during examination or measurement and breach of confidentiality. Equipment will be cleaned or disinfected according to institutional procedures, measurements will be performed by trained staff, and study data will be coded and stored securely.

Adverse events related to study procedures are expected to be rare. Any skin abnormality requiring medical attention identified during the study will be recorded and managed according to usual care. Serious adverse events related or possibly related to study procedures will be reported to the principal investigator and ethics committee within 24 hours according to institutional requirements.

13. Ethical Considerations

The study has received ethics approval from the Ethics Committee of the Children's Hospital, Zhejiang University School of Medicine, approval number 2025-IRB-0077-P-01. The study will be conducted in accordance with the approved protocol, applicable institutional requirements, and ethical principles for research involving human participants. Written informed consent will be obtained before study-specific procedures. Personal identifiers will be protected, and public documents should be redacted where appropriate before upload to ClinicalTrials.gov or other public platforms.

14. Dissemination Plan

The investigators plan to publish one to two academic papers, including at least one SCI-indexed paper if feasible. The study may also support development of expert consensus materials and educational manuals for insulin pump-related skin care in children with T1D. Findings will be disseminated through academic conferences and institutional reporting after completion of data analysis.

15. References

16. National Center for Metabolic Diseases Clinical Research Center (Changsha), China Type 1 Diabetes Alliance. Expert consensus on self-management education and support for type 1 diabetes (2023 edition). Chinese Journal of Diabetes Mellitus. 2023;15(8):679-689.
17. Sun H, Saeedi P, Karuranga S, et al. IDF Diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. Diabetes Research and Clinical Practice. 2022;183:109119.

18. Li GH, et al. Clinical incidence and characteristics of newly diagnosed type 1 diabetes in Chinese children and adolescents: a nationwide registry study of 34 medical centers. Frontiers in Pediatrics. 2022;10.
19. Chinese Diabetes Society and related expert groups. Guideline for the diagnosis and treatment of type 1 diabetes in China (2021 edition). Chinese Journal of Diabetes Mellitus. 2022;14(11):1143-1250.
20. Passanisi S, Salzano G, Lombardo F. Skin involvement in paediatric patients with type 1 diabetes. Current Diabetes Reviews. 2022;18(4):e030921196145.
21. Chen X, Wu X, Yuan T, et al. Prevalence of skin problems caused by insulin pump therapy and associated factors in children with type 1 diabetes mellitus: a large cross-sectional survey in China. Diabetes Research and Clinical Practice. 2024;212:111714.

Appendix A. Parent/Guardian and Caregiver Informed Consent Form

Study title: Factors Associated with Insulin Pump-Related Skin Complications in Children with Type 1 Diabetes: A Cross-sectional Study

Principal investigator: Xiaochun Chen, Department of Endocrinology, Children's Hospital, Zhejiang University School of Medicine

Ethics approval number: 2025-IRB-0077-P-01

A1. Invitation to Participate

You and your child are invited to take part in a research study. Before you decide whether to participate, please read this form carefully. The researcher will explain the study to you and answer any questions. Participation is voluntary.

A2. Why is this study being done?

Children with type 1 diabetes often need long-term insulin pump therapy. Some children develop skin problems at infusion sites, such as redness, itching, infection, scarring, lipohypertrophy, or lipoatrophy. This study aims to understand how common these skin problems are and what factors may be related to them, including skin and subcutaneous fat thickness, pump-use habits, and caregiver skin-care knowledge and practices.

A3. Who can participate?

Children diagnosed with type 1 diabetes who have used an insulin pump for at least 6 months may be eligible. The child's primary caregiver may also participate by completing questionnaires. The researcher will confirm whether you and your child meet the study criteria.

A4. What will happen if we participate?

- You will complete questionnaires about your child's general information, insulin pump use, skin-care knowledge, attitudes, and practices, and related health information.
- Your child's skin at common insulin pump sites may be examined by trained staff.
- Skin and subcutaneous fat thickness may be measured at the arms, abdomen, buttocks, and thighs using non-invasive ultrasound and skinfold calipers.
- If you agree, photographs of skin findings may be taken using the study code and used only for research assessment and quality control.
- No experimental treatment will be given. Your child's usual medical care will not be changed.

A5. How long will participation take?

This is a one-time cross-sectional assessment. Participation is expected to take approximately 20 to 40 minutes. There is no required study follow-up.

A6. What are the possible risks or discomforts?

The procedures are non-invasive. Your child may experience mild temporary discomfort during skinfold measurement or skin examination. There is also a small risk of loss of confidentiality. The research team will protect privacy by using study codes and secure data storage.

A7. Are there any benefits?

You and your child may not receive direct medical benefit. If a skin problem is found, the research team may provide skin-care advice or recommend clinical evaluation according to usual care. The study may help improve future education and skin-care strategies for children using insulin pumps.

A8. Will participation affect medical care?

No. Participation is voluntary. Refusing to participate or withdrawing from the study will not affect your child's current or future medical care, relationship with clinicians, or access to treatment.

A9. Confidentiality

Your child's and your personal information will be kept confidential as required by law and institutional policy. Research data will be coded and stored securely. Only authorized study staff, the ethics committee, or regulatory authorities may review study records when necessary. If study results are published, no information that directly identifies you or your child will be disclosed.

A10. Voluntary Participation and Withdrawal

You may decide not to participate or may withdraw at any time without giving a reason. If you withdraw, no new study data will be collected. Data already collected before withdrawal may be used in coded form unless you request otherwise and unless deletion is not permitted by applicable research integrity requirements.

A11. Costs and Compensation

There is no additional cost to you for participating in this study. A diabetes education booklet or similar educational material may be provided after completion of the assessment, according to the local study plan.

A12. Contact Information

If you have questions about the study, please contact the study investigator at the Department of Endocrinology, Children's Hospital, Zhejiang University School of Medicine. For questions about participant rights, please contact the institutional ethics committee. Publicly posted versions should remove personal phone numbers, direct emails, signatures, and other identifiers as appropriate.

A13. Consent Statement

I have read this informed consent form, or it has been read to me. I have had the opportunity to ask questions, and my questions have been answered. I understand that participation is voluntary and that I may withdraw at any time without affecting my child's medical care. By signing below, I agree for myself and/or my child to participate in this study as described above.

Name of child participant: _____

Name of parent/legal guardian: _____

Signature of parent/legal guardian: _____

Date: _____

Name of caregiver participant if different from guardian: _____

Signature of caregiver participant: _____

Date: _____

Name of investigator obtaining consent: _____

Signature of investigator: _____

Date: _____

Appendix B. Child Assent Form (Age-Appropriate Template)

We are asking you to join a study about skin problems that can happen when children use insulin pumps. If you join, we may look at your skin where the pump is used, measure the thickness of your skin and the fat under the skin

using a small ultrasound device and calipers, and ask you or your caregiver some questions. This will not change your usual treatment.

You do not have to join. If you say no, your doctors and nurses will still take care of you as usual. If you join and later want to stop, you can stop at any time. You can ask questions whenever you want.

I have had the study explained to me. I know I can ask questions and can stop at any time. I agree to take part in this study.

Name of child: _____

Signature or mark of child: _____

Date: _____

Name of person explaining the study: _____

Signature: _____

Date: _____

Appendix C. ClinicalTrials.gov Document Upload Checklist

- Confirm Official Title, brief title, study design, number of sites, and sample size are consistent across protocol, IRB approval, and PRS registration fields.
- Use the most recent IRB-approved protocol and consent documents for public posting.
- Add the NCT number to the cover page after it is assigned.
- Redact personal identifiers, private phone numbers, direct emails, signatures, and any information not appropriate for public posting.
- Convert the final documents to PDF/A format before upload if required by the PRS document section.
- Confirm whether the SAP is included within the protocol or uploaded as a separate document.