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TITLE PAGE

Title:

Canadian Anaphylaxis Network- Predicting Recurrence after Emergency Presentation for Allergic REaction (CAN-PREPARE): A Prospective, Cohort Study Protocol

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ABSTRACT:

Introduction

Anaphylaxis is a severe, potentially fatal multi-organ system manifestation of an allergic reaction. The highest incidence of anaphylaxis is in children and adolescents. Biphasic anaphylaxis (BA) is defined as the recurrence of allergic symptoms after resolution of an initial reaction. It has been reported to occur in 10-20% of cases within 1-48hours from the onset of the initial reaction. The dilemma for physicians is determining which patients with resolved anaphylaxis should be observed for BA, and for how long. Guidelines for duration of post-anaphylaxis monitoring vary, are based on limited evidence, and can have unintended negative impacts on patient safety, quality of life, and healthcare resources. The objectives of this study are to derive a prognostic model for BA and to develop a risk-scoring system that informs disposition decisions of children who present to emergency departments (ED) with anaphylaxis.

Methods and Analysis

This prospective multi-centre cohort study will enroll 1,682 patients from seven pediatric EDs that are members of the Pediatric Emergency Research Canada network. We will enroll patients younger than 18 years of age with an allergic reaction meeting anaphylaxis diagnostic criteria. Trained ED research assistants will screen, obtain consent, and prospectively collect study data. Research assistants will follow patients during their ED visit and ascertain, in conjunction with the medical team, if the patient develops BA. A standardized follow-up survey conducted following study enrollment will determine if a biphasic reaction occurred after ED disposition. Model development will conform to the broad principles of the PROGRESS (Prognosis Research Strategy) framework and reporting will follow the TRIPOD Statement.

Ethics and Dissemination

All sites will obtain institutional Research Ethics Board approval. Our dissemination plan focuses on informing clinicians, policy-makers, and parents of the results through publication in peer-reviewed journals and broadcasting on multiple media platforms.

Registration Details

ClinicalTrials.gov (NCT05135377).

Article Summary:

Strengths and limitations of this study:

1) Largest prospective cohort study on pediatric biphasic anaphylaxis conducted to-date.
2) Sample size calculation and statistical analysis plan are based on the highest methodological standard for prediction modelling research.
3) We established an international, multidisciplinary expert team encompassing pediatrics, emergency medicine, allergy/immunology, research methodology and statistics, and knowledge translation.
4) We instituted an advisory council of external parents, youth, and clinicians end-users and community partners to monitor milestones, identify potential barriers and enablers for future implementation, and guide future decision aid tools.
5) This study is not designed to generalize our findings to settings outside of an academic pediatric emergency department; this limitation may be mitigated when we yield a clinically useful and statistically sensitive model that may be externally validated.

INTRODUCTION:

Anaphylaxis is the most severe form of allergic reaction that rapidly affects multiple body systems and can be fatal.[1,2] The highest incidence is in children and adolescents.[3–8] In Canada, approximately every 10 minutes, there is an Emergency Department (ED) visit for food allergy.[9,10] Up to 80% of anaphylactic reactions in children are triggered by food,[11] and 8% of allergy-related ED visits are due to anaphylactic shock.[3]

According to the Canadian Institute for Health Information, the rate of children visiting Ontario and Alberta EDs for anaphylaxis more than doubled between 2007 and 2014.[3] Among 13- to 17-year-olds, ED visits increased significantly (from 23/100,000 in 2007 to 59/100,000 in 2014). The highest annual rate of ED visits was among children aged 4 and younger.[3] Similarly, the Cross-Canada Anaphylaxis Registry reported a steady increase in pediatric ED visits: from 1.8/1000 in 2011 to 4.5/1000 in 2015.[10,12] These estimates are higher than data from the US and Europe.[13,14]

As the volume of anaphylaxis-related ED visits continues to rise,[10,12] ambiguity in how physicians manage anaphylaxis increases the healthcare burden and may contribute to ED crowding. Current Canadian and international guidelines recommend that all patients with anaphylaxis present to the ED, and after initial reactions have been treated, remain there for a prolonged period to be monitored for biphasic anaphylaxis (BA, also called delayed or late-phase anaphylaxis).[15–17] BA is a second wave of symptoms after initial resolution.[18,19] The reported incidence of this potentially serious phenomenon varies from 10-20%; the majority occur within 1-24 hours from onset of the initial reaction.[16–47] The dilemma for ED

physicians is to determine which patients should be observed and the optimum duration of observation.[48] Guidelines for post-anaphylaxis care vary,[1,16,17] are based on poor or little evidence, and have negative impacts on patient safety and quality of life.[18,36,49,50] This clinical uncertainty originates from the lack of validated clinical predictors for BA. Consequently, many children are hospitalized or undergo prolonged monitoring in the ED after resolution of initial anaphylaxis.[50,51]

In the United States, ED care and hospitalizations are the largest drivers of annual direct medical costs ($1.9 billion) for food allergic children.[52] The incremental cost of extended ED observation of resolved anaphylaxis (6 hours versus 1 hour) is $62,374 USD per case of BA identified ($68,411 USD from the societal perspective). ED monitoring beyond 6 hours of patients who quickly stabilize after treatment is associated with an incremental cost-effectiveness ratio of $230,202 per case observed (societal perspective).[53] As ED crowding and visits for anaphylaxis increase, current post-anaphylaxis clinical practice is neither sustainable nor cost-effective.[29]

Providing the best evidence-based value care at the lowest cost is critical to optimize resource stewardship and eliminate wasteful spending in healthcare. In alignment with national and international research priorities,[54–58] our goal is to derive a prognostic clinical prediction model that identifies children with anaphylaxis who are at heightened risk of BA. This model will address a gap in current knowledge and practice, with anticipated benefits for patient care and health system efficiency worldwide.

METHODS AND ANALYSIS:

Study Design

We will conduct a prospective multi-centre cohort study. Prospective data collection is necessary to minimize research waste in prediction modelling, accurately assess the risk and impact of BA on patients and the healthcare system, and derive a clinically useful prediction rule. Our design ensures consistency and precision of data collection of all clinically relevant potential predictors and enables accurate assessment of critical outcomes. Our methods follow established guidelines for developing clinical prediction rules.[59–68] We conform to the PROGRESS (Prognosis Research Strategy) methods of prediction modelling.[66,69–71]

Study Population

All children aged 0–17 years who present to a participating ED will be screened for study enrollment based on the following criteria:

Inclusion Criteria

1. Age < 18 years
2. Presenting to ED with an allergic reaction that matches diagnostic criteria for anaphylaxis as defined by the World Allergy Organization (WAO) in 2019.[72] *Anaphylactic reaction* is a multi-system allergic reaction characterized by one or more clinical features involving the respiratory or cardiovascular systems and associated with one or more clinical features involving the skin or gastrointestinal tract. These criteria are universally accepted and endorsed by most international allergy and emergency medicine

organizations.[15,54,73] The 2019 WAO guidelines clarify the involvement of two organ systems is not always requisite for diagnosis: "Although the diagnosis of anaphylaxis usually depends on the involvement of multiple organ systems, anaphylaxis may present as an acute cardiac or respiratory event as the only manifestation of anaphylaxis."[72] Thus, an individual with isolated hypotension, bronchospasm, or upper airway obstruction after exposure to a known or potential trigger will be deemed to have anaphylaxis, even if typical skin features are absent.[72,74]

3. Language proficiency in English or French

Exclusion Criteria

1. Anaphylactic reaction that occurred in the context of a suicidal attempt or intoxication.
2. Anaphylactic reaction that began in hospital and managed outside the ED (inpatient or outpatient unit)
3. Inability or unwillingness of individual and/or caregiver to complete the follow-up surveys post ED discharge.

Study Setting

The study will enrol participants in EDs from seven hospitals: CHU Sainte-Justine, Children's Hospital of Eastern Ontario, Hospital for Sick Children, McMaster Children's Hospital, Children's Hospital – London Health Sciences Centre, Alberta Children's Hospital, and Stollery Children's Hospital. These EDs are members of Pediatric Emergency Research Canada (PERC; https://www.perc-canada.ca)[75]. Research staff will follow site-specific Research Ethics

Boards' (REB) guidelines for approaching potential participants and families for research studies, screening for eligibility, and obtaining consent.

Outcome

The primary outcome is development of BA. As per the recently published consensus definition,[76] to be classified as BA, an anaphylactic reaction must meet three criteria: 1) initial anaphylactic reaction followed by resolution of all initial manifestations for ≥1 hour, with no new symptoms or treatment administered in that time; 2) second phase of new or recurrent symptoms or signs that meet the consensus definition of anaphylaxis occurring within 1-48 hours from complete resolution of initial symptoms or signs; and 3) new or recurrent symptoms or signs not caused by antigen re-exposure.[35] We will capture any new or recurrent symptoms or signs, but only clinical manifestations that meet diagnostic criteria for anaphylaxis will be defined as **anaphylactic biphasic responses**. This definition focuses on *clinically important* or major biphasic reactions.[29,30] Mild symptoms that involve only the skin (e.g., urticarial rash) will be captured and classified as minor biphasic responses, but they do not meet our case definition for BA.

Data collection in ED

A research assistant (RA) or research nurse (RN) in the ED will approach potential participants to screen for eligibility and provide a study overview. When the pre-screen has been completed, the RA/RN will consult with the attending physician to confirm that the symptoms are consistent with anaphylaxis. If the attending physician considers the signs and symptoms to be more in line with another diagnosis (e.g., gastroenteritis), the patient will be excluded. After confirming

participant eligibility, the RA/RN will obtain written informed consent (and assent as appropriate) and proceed with data collection. Table 1 lists the independent variables that will be collected.

Table 1: Data collection variables

From clinical history	• Demographics: age, sex, date of birth, and self-identified race • Past medical history (e.g., cardiac disease, bronchial asthma, eczema) • Previous ED visits for anaphylaxis • Current anaphylaxis augmenting factors (e.g., physical exercise, viral illness or fever, menses in female, drugs such as non-steroidal anti-inflammatory drugs (NSAID), antacid, ß-blockers, and ACE inhibitors) • Allergen trigger (e.g., type, time of exposure and onset of symptoms, location)
From physical examination	• Participant weight • Vital signs at triage (heart rate, respiratory rate, blood pressure, and oxygen saturation) • Triage score (based on Canadian Pediatric Triage and Acuity Scale) • Physical exam findings upon arrival at ED
From pre-hospital and initial ED intervention, and disposition	• Treatment interventions (e.g., epinephrine, bronchodilators, etc.) received before arrival at ED and during transport by paramedics (if applicable) • Non-pharmacologic/supportive interventions (such as intubation and intravenous fluids) and timeline • Pharmacologic interventions (including dose, route, frequency, and time administered) • Disposition time, location (home or hospitalization), list of discharge medications, and outpatient allergy referral
From ED monitoring period	• Presence and description of new/recurrent symptoms/signs • Time of new recurring symptoms/signs • Management interventions given for biphasic reaction
From follow-up email/phone call after ED disposition	• Presence and description of new/recurrent symptoms/signs • Time of new/recurrent symptoms/signs • Management interventions given for biphasic reaction, including visits to ED/primary care providers
From 6-month follow-up (if applicable)	• If patient was seen by Allergist • If seen by Allergist, was allergic agent identified?

The RA/RN will review the physical exam findings with the clinical team (treating ED physician/bedside nurse). Because anaphylaxis is a clinical diagnosis, participants or caregivers will be asked about the spectrum of symptoms and signs experienced before and upon arrival in the ED. The RN/RA will verbally administer a structured questionnaire to participants or caregivers to collect demographics, medical history, risk factors, reaction characteristics, and symptoms. Information from the participant and from the medical record about treatment before and after ED arrival, and biphasic anaphylaxis events during the ED monitoring period, will by captured by the RN/RA. Missing data will be obtained by questioning the participant, caregiver, or treating ED team. To capture all BA events and ascertain symptom recurrence while participants are being monitored, the research RN/RA will follow the participant/caregiver throughout the ED visit. Events occurring outside study team hours will be captured in the follow-up questionnaire.

First follow-up after ED discharge or hospital admission

Published data have reported symptom recurrence up to 48 hours from anaphylaxis onset.[28,44] We will contact participants by telephone or email 2-5 days after enrollment to complete a standardized questionnaire that will capture the nature and timing of new and recurrent symptoms or signs, follow-up with health providers, return ED visits, and treatments received. Events that took place in-hospital, but were not previously captured by the study team (e.g., outside study team hours), will be verified from the participant's medical chart.

Second follow-up after ED discharge or hospital admission

Participants whose anaphylaxis trigger or culprit allergen was unknown at the time of study enrollment will be contacted 6-9 months after enrollment. We will determine if the participant had been assessed by an allergy specialist in the interim, and if so, whether an allergic agent had been identified.

Strategies for retention

For the follow-up survey, the families of participants will be asked: (1) their preferred mode of contact (email or telephone), and (2) the best time to reach them and contact number. Based on their preferences, we will send the follow-up questionnaire as an automated REDCap survey to the parent/caregiver email address or administer the survey by telephone. If the e-survey is not completed within 24 hours, a second email will be sent. If there is no response to a second email, experienced staff will contact the participant for a telephone interview. A similar schedule of repeat calls will be used to reach those who selected telephone follow-up.

Sample Size

Based on our earlier research and estimates from well-designed adult and pediatric studies,[28,35] 10% is a conservative of the population-wide event rate for BA. Our systematic reviews of potential predictors [77] and other relevant studies identified 19 potential predictive variables.[78] Recent *BMJ* and *Stat in Med* articles offer practical guidance for calculating the sample size required for the development of clinical prediction models.[79,80] Following these guidelines, we considered sample size from four perspectives, with the largest being selected as the sample size needed. The four calculations are based on: the approximate 95% confidence

interval for the overall outcome proportion 0.10 in the study population (calculated sample size needed n=139); the mean absolute prediction error of the average error in the model's outcome (n=274); achievement of an expected uniform shrinkage factor of ≤10% (n=1,529); and ensuring a small, expected optimism in the apparent proportion of overall variation explained R2 (n=719). Details of these calculations with the selection of the parameter estimates and sensitivity considerations are provided in **Supplementary Material A.** Taking the largest sample size that meets all four criteria, we need to enroll 1,529 participants with anaphylaxis. Based on previous studies by our network, we anticipate 10% loss to follow-up.[81,82] Thus, our estimated sample size is 1,682 participants.

Dependent Predictors Selection for Analysis

Table 2 lists the 19 candidate-dependent predictors that we will include in the analysis. We chose these 19 variables based on clinical studies of predictors of BA by our team and by others,[16–47] two systematic reviews,[77,83] the meta-analysis from the 2020 anaphylaxis practice parameter,[84] and clinical experience. These predictors encompass recently published BA predictors from the European Anaphylaxis Registry retrospective data.[85] Given the direct association between initially severe anaphylaxis and subsequent BA, we also include risk factors of severe anaphylaxis.[86]

Table 2: Candidate-dependent predictors that will be included in the analysis for primary objective of study, based on previous clinical studies on BA predictors

Allergen predictors	**Patient predictors**
Peanut trigger [85]	Age [34,35,38,86]
Venom trigger [86]	Male sex [86,87]
Drug trigger [11,78,84,86–89]	Previous anaphylaxis [31,36,39]
Unknown trigger [31,39,83–85]	Pre-existing asthma or chronic lung disease [26,28,42,47,86,87,89]
≥30 min from exposure to trigger to onset of symptoms [43,85]	Exercise as co-factor for anaphylaxis [1,86,90–93]
Disease predictors	**Treatment predictors**
Signs of severe anaphylaxis* [22,23,25,27,34,38,83,84,94]	Treatment of initial reaction with >1 dose of epinephrine [22,23,35,42,45,46,84,95]
Wide pulse pressure [84,95]	Treatment of initial reaction with epinephrine [34,35,44,96]
Respiratory distress or wheezing [31,35,97]	Systemic steroids [44,84]
Gastrointestinal manifestations [83,85]	Epinephrine administration >60 min from onset of reaction [20,26,35,39,98,99]
Cutaneous manifestations [69, 73]	
*Include (as defined by Brown's severity grading score)[100]: cyanosis or SpO2 ≤ 92%, hypotension, confusion, collapse, loss of consciousness, or incontinence.	

Data analysis

Descriptive analysis will be used to summarize baseline participant demographics, anaphylaxis clinical manifestations, and management characteristics. Although race and indigenous status will be collected as demographic characteristics, we will not perform race-based analysis; these variables will be used as descriptors to demonstrate the diversity and representativeness of our sample.

Multivariable regression analysis will be used to derive a predictive model for BA. As recommended by Royston *et al.*[101], our modelling strategy will follow six steps.

1) *Evaluate data quality*. Predictors found to be complete (<10% missing data) will be used in a full model approach. Missing data will be considered Missing at Random. If any potential predictor has >10% missing value, a multiple imputation procedure will be followed to replace these values.[61,64] If >50% data are missing, the variable will be omitted from the analysis.

2) *Handle and model continuous predictors*. To maximize the predictive ability of the regression model, we will maintain continuous variables such as age.[102,103] A multivariable fractional polynomial procedure will be used to identify and model nonlinear continuous variables. Our a priori categorization of some originally continuous predictors, such as "time to epinephrine treatment," is based on plausible clinical and basic science research [77,104,105] and recent regression analysis.[39]

3) *Develop final model (predictor selection)*. Predictors that match the above two criteria will be entered in a "full model" that contains the main effects of all candidate predictors. The objective of predictors reduction is to find the best combinations of variables for accurate prediction (low mean squared error) in a model that is easy for clinicians to use and that contains as few variables as possible. Therefore, we will assess for collinearity and use shrinkage technique as a method of variable reduction.[68] Collinearity between predictors will be evaluated with correlation coefficient (r) and variance inflation factors (VIF), which measure the degree to which collinearity degrades the precision of estimate coefficients. Strongly correlated predictors ($r > 0.8$, or $VIF > 10$) will be combined in a single variable. In accordance with Harrell and Steyerberg, we will use Penalized maximum likelihood (PML) estimation to perform shrinkage reduction (reduction of the regression coefficients to improve prediction quality). Maximizing a modified Akaike's Information Criterion will be

used to choose the optimal penalty factor for PML and select the best model. This approach includes a penalty against large models to deal with the trade-off between overfitting and model simplicity.[101] The added benefit of this approach is that we could use more penalty factor if we found significant interaction.

4) *Assess model performance with three measures* [64,106,107]

   a. *Calibration* refers to the accuracy of absolute risk estimates.[106] Model calibration will be assessed by calibration slope, and graphically, by locally weighted scatterplot smoothing (LOESS) plots of observed versus predicted probabilities of the outcome. The slope of the calibration curve is a measure of over-optimism of the model predictions.

   b. *Discrimination* will be assessed by the receiver operating characteristics curve and the concordance (C) index, which measures how well the model discriminates between participants with and without BA.

   c. *Clinical usefulness* of the prediction model will be assessed using net benefit as a decision analytic.[107,108] The derived prediction rule will be cross-validated by comparing the classification of each participant with their actual primary outcome status.

5) *Validate model*

   i. *Internal validation.* Recruiting from geographically separated sites enhances generalizability and supports internal validation of the model.[61,109,110] To correct for overfitting and quantify optimism in model performance, our model will be validated internally using bootstrapping through the following steps: [102,111,112]

1) After developing the prediction model using the entire original sample and determining apparent performance, we will generate a bootstrap sample by sampling individuals with replacement from the original sample; 2) Develop a model using the bootstrap sample (applying the same modelling and predictor selection in step 3 above); 3) Determine the apparent bootstrap performance of this model (performance of bootstrap model in the original sample and calculate the optimism as the difference between bootstrap performance and test performance); 4) Repeat steps 1 through 3 at least 500 times; and 5) Average the estimates of optimism in step 4, and subtract the value from the apparent performance obtained in step 1 to obtain an optimism-corrected estimate of performance.

ii. *External validation*: Before broad clinical implementation, our derived rule requires external validation. Lack of external validation is a limitation of many clinical prediction models.[77,113] For two reasons, this proposal focuses only on model derivation: 1) Requesting funding for external validation may be premature. Before embarking on external validation, we need proof that our *a priori* risk factors yield a clinically useful and statistically sensitive model. 2) The validation phase should be broader, in different settings, with other participants, and with different clinicians.[114,115] Our ultimate goal is to validate our model and risk score in an international setting. Such validation is feasible because PERC is a member of the Pediatric Emergency Research Networks (PERN), and member networks have a history of collaboration.[81,82,116]

6) *Present model*. As described by Sullivan *et al.*[117], we will use the regression coefficient in our final fitted model to generate a clinical decision rule that enables point-of-care risk

assessment of BA. To develop a points score system, we will follow the steps described in a recent *BMJ* paper: [118] 1) Multiply and round regression coefficients of binary predictors; 2) Search for score for continuous predictors to determine the difference in regression units; 3) Estimate multiplication factor for the scores; 4) Use decision curve analysis to assign participants to risk groups and quantify any deterioration in discriminative performance; and 5) Present accompanying table of probabilities to allow points score to be translated into a predicted risk. The anticipated stoplight scoring system (green=low→discharge; yellow=moderate→monitor in ED/preference-sensitive care; red=high→admit to hospital) will inform evidence-based disposition decisions by clinicians and anticipatory guidance to families.

Patient and Public Involvement

Patients and/or the public were involved in the design and dissemination plans for this research. To promote uptake of our results, potential knowledge users have been and will be engaged throughout the project.[119] We have a multi-phase approach to maximize collaboration and opportunities for diverse knowledge users to interact at various research phases.[120] Our multi-site team includes ED clinicians as typical end-users and champions for future implementation. We have established an advisory council of external end-users (parents, youth, ED clinicians) and community partners (Food Allergy Canada, Canadian Society of Allergy & Clinical Immunology) to monitor milestones, identify potential barriers and enablers for future implementation, and guide future decision aids study. The leadership team at Food Allergy Canada has reviewed and supports this proposal. To improve study operation and minimize the

burden on patients and families, we sought feedback from the Patients and Families Advisory Committee at the Children's Hospital of Eastern Ontario Research Institute.

ETHICS AND DISSEMINATION:

Ethics

Approval will be obtained from ethics boards at all recruiting centers. Ethics approval has been received from Clinical Trials Ontario (CTO 3721) for the hospitals in Ontario. Written informed consent, and/or assent when appropriate, will be obtained from all participants or legal guardians.

The study is registered at ClinicalTrials.gov (NCT05135377). Results information from this study will be submitted to ClinicalTrials.gov.

End-of-grant KT (Knowledge Translation)

ED personnel, providers, allergists, clinical researchers, administrators, and government policy-makers can use our study outputs to improve healthcare delivery. KT will focus on informing clinicians, other key user groups, and parents and participants. Our plan has three goals: increase knowledge awareness, inform/change practice, and inform future research.[121,122]

We have a powerful infrastructure to disseminate our results. Study investigators are senior members of PERC and PERN, networks that include pediatric ED researchers worldwide (>100 hospitals across 6 PERN networks)[123], practicing clinicians, medical educators, and healthcare administrators. PERC is closely tied to the TREKK (Translating Emergency Research

Knowledge for Kids) Network of Centres of Excellence,[124] a partnership for knowledge exchange between general EDs and PERC sites. Our reporting/publication of the study results will conform to the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) checklist.[112]

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COMPETING INTERESTS STATEMENT:

All authors have read and understood BMJ policy on declaration of interests and have no relevant interest to declare. Dr Amy C. Plint is supported by a Tier I University of Ottawa Research Chair. Dr. Stephen Freedman is supported by the Alberta Children's Hospital Professorship in Child Health and Wellness.

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AUTHORS' CONTRIBUTIONS:

WA and ACP conceived the study idea. WA, ACP, and MS wrote the protocol with input from all authors. All authors provided input into the methodology and analysis plan. All authors approved the final protocol manuscript. ACP and GW are the supervisors of the study.

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SUPPLEMENTARY MATERIAL:

Supplementary Material A - Sample Size Calculation

Following (Riley 2019, Riley 2020), the sample size is considered from four perspectives, and the largest sample size calculated is selected as the overall sample size needed.

1. Approximate 95% confidence interval for overall outcome proportion in study population

$$n = \left(\frac{1.96}{\delta}\right)^2 \hat{\theta}(1-\hat{\theta})$$

$\hat{\theta} = .10$ *or* $.15$ - overall outcome proportion in study population

Then for:

$\hat{\theta} = .10$, n=139

$\hat{\theta} = .15$, n=196

2. Mean absolute prediction error (MAPE) - average error in the model's outcome

$$n = \exp\left(\frac{-0.508 + 0.259\ln(\theta) + 0.504\ln(P) - \ln(MAPE)}{0.544}\right)$$

MAPE=0.050 - suggested MAPE is no larger than 0.050 (lower values in settings may be appropriate where precise predictions are needed if consequences of wrong decisions are large)

P=18 - number of predictors

For $\hat{\theta} = .10$, then n=274

For $\hat{\theta} = .15$, then n=332

3. Achieve expected uniform shrinkage factor S

$$n = \frac{P}{(S-1)ln\left(1-\frac{R^2_{cs}}{S}\right)}$$

R^2_{cs} =0.10 or 0.50 - proportion of overall variation explained

P=19 - number of predictors

S=0.9 or 0.85 - suggested target for shrinkage of ≤10% (i.e. S≥0.9)

For $R^2_{cs} = 0.10$, $S = 0.9$, then n=1529

For $R^2_{cs} = 0.15$, $S = 0.9$, then n=988

For $R^2_{cs} = 0.10$, $S = 0.85$, then n=959

For $R^2_{cs} = 0.15$, $S = 0.85$, then n=1529

4. Ensure a small expected optimism in apparent R^2

$$n = \frac{P}{(S-1)ln\left(1-\frac{R^2_{cs}}{S}\right)}$$

Where

$$S = \frac{R^2_{cs}}{R^2_{cs} + \delta \max\left(R^2_{cs}\right)}$$

$$\max(R^2_{cs}) = 1 - exp\left(\frac{2lnL_{null}}{n}\right)$$

$$lnL_{null} = Eln\left(\frac{E}{n}\right) + (n-E)ln\left(1-\frac{E}{n}\right)$$

and consider $\frac{E}{n} = \theta$

For $\hat{\theta} = .10$, $R^2_{cs} = 0.10$ then $\max(R^2_{cs})$ =0.48, S=0.81 and n=719

For $\hat{\theta} = .10$, $R^2_{cs} = 0.15$ then $\max(R^2_{cs})$ =0.48, S=0.81 and n=463

For $\hat{\theta} = .15$, $R^2_{cs} = 0.10$ then $\max(R^2_{cs})$ =0.57, S=0.84 and n=888

For $\hat{\theta} = .15$, $R^2_{cs} = 0.15$ then $\max(R^2_{cs})$ =0.57, S=0.84 and n=572

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TITLE PAGE

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Canadian Anaphylaxis Network- Predicting Recurrence after Emergency Presentation for Allergic REaction (CAN-PREPARE): A Prospective, Cohort Study Protocol

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ABSTRACT:

Introduction

Anaphylaxis is a severe, potentially fatal multi-organ system manifestation of an allergic reaction. The highest incidence of anaphylaxis is in children and adolescents. Biphasic anaphylaxis (BA) is defined as the recurrence of allergic symptoms after resolution of an initial reaction. It has been reported to occur in 10-20% of cases within 1-48 hours from the onset of the initial reaction. The dilemma for physicians is determining which patients with resolved anaphylaxis should be observed for BA, and for how long. Guidelines for duration of post-anaphylaxis monitoring vary, are based on limited evidence, and can have unintended negative impacts on patient safety, quality of life, and healthcare resources. The objectives of this study are to derive a prognostic model for BA and to develop a risk-scoring system that informs disposition decisions of children who present to emergency departments (ED) with anaphylaxis.

Methods and Analysis

This prospective multi-centre cohort study will enroll 1,682 patients from seven pediatric EDs that are members of the Pediatric Emergency Research Canada network. We will enroll patients younger than 18 years of age with an allergic reaction meeting anaphylaxis diagnostic criteria. Trained ED research assistants will screen, obtain consent, and prospectively collect study data. Research assistants will follow patients during their ED visit and ascertain, in conjunction with the medical team, if the patient develops BA. A standardized follow-up survey conducted following study enrollment will determine if a biphasic reaction occurred after ED disposition. Model development will conform to the broad principles of the PROGRESS (Prognosis Research Strategy) framework and reporting will follow the TRIPOD Statement.

Ethics and Dissemination

All sites will obtain institutional Research Ethics Board approval. Our dissemination plan focuses on informing clinicians, policy-makers, and parents of the results through publication in peer-reviewed journals and broadcasting on multiple media platforms.

Registration Details

ClinicalTrials.gov (NCT05135377).

Article Summary:

Strengths and limitations of this study:

1) Largest prospective cohort study on pediatric biphasic anaphylaxis conducted to-date.
2) Sample size calculation and statistical analysis plan are based on the highest methodological standard for prediction modelling research.
3) We established an international, multidisciplinary expert team encompassing pediatrics, emergency medicine, allergy/immunology, research methodology and statistics, and knowledge translation.
4) We instituted an advisory council of external parents, youth, and clinicians end-users and community partners to monitor milestones, identify potential barriers and enablers for future implementation, and guide future decision aid tools.
5) This study is not designed to generalize our findings to settings outside of an academic pediatric emergency department; this limitation may be mitigated when we yield a clinically useful and statistically sensitive model that may be externally validated.

INTRODUCTION:

Anaphylaxis is the most severe form of allergic reaction that rapidly affects multiple body systems and can be fatal.[1,2] The highest incidence is in children and adolescents.[3–8] In Canada, approximately every 10 minutes, there is an Emergency Department (ED) visit for food allergy.[9,10] Up to 80% of anaphylactic reactions in children are triggered by food,[11] and 8% of allergy-related ED visits are due to anaphylactic shock.[3]

According to the Canadian Institute for Health Information, the rate of children visiting Ontario and Alberta EDs for anaphylaxis more than doubled between 2007 and 2014.[3] Among 13- to 17-year-olds, ED visits increased significantly (from 23/100,000 in 2007 to 59/100,000 in 2014). The highest annual rate of ED visits was among children aged 4 and younger.[3] Similarly, the Cross-Canada Anaphylaxis Registry reported a steady increase in pediatric ED visits: from 1.8/1000 in 2011 to 4.5/1000 in 2015.[10,12] These estimates are higher than data from the US and Europe.[13,14]

As the volume of anaphylaxis-related ED visits continues to rise,[10,12] ambiguity in how physicians manage anaphylaxis increases the healthcare burden and may contribute to ED crowding. Current Canadian and international guidelines recommend that all patients with anaphylaxis present to the ED, and after initial reactions have been treated, remain there for a prolonged period to be monitored for biphasic anaphylaxis (BA, also called delayed or late-phase anaphylaxis).[15–17] BA is a second wave of symptoms after initial resolution.[18,19] The reported incidence of this potentially serious phenomenon varies from 10-20%; the majority occur within 1-24 hours from onset of the initial reaction.[16–47] The dilemma for ED

physicians is to determine which patients should be observed and the optimum duration of observation.[48] Guidelines for post-anaphylaxis care vary,[1,16,17] are based on poor or little evidence, and have negative impacts on patient safety and quality of life.[18,36,49,50] This clinical uncertainty originates from the lack of validated clinical predictors for BA. Consequently, many children are hospitalized or undergo prolonged monitoring in the ED after resolution of initial anaphylaxis.[50,51]

In the United States, ED care and hospitalizations are the largest drivers of annual direct medical costs ($1.9 billion) for food allergic children.[52] The incremental cost of extended ED observation of resolved anaphylaxis (6 hours versus 1 hour) is $62,374 USD per case of BA identified ($68,411 USD from the societal perspective). ED monitoring beyond 6 hours of patients who quickly stabilize after treatment is associated with an incremental cost-effectiveness ratio of $230,202 per case observed (societal perspective).[53] As ED crowding and visits for anaphylaxis increase, current post-anaphylaxis clinical practice is neither sustainable nor cost-effective.[29]

Providing the best evidence-based value care at the lowest cost is critical to optimize resource stewardship and eliminate wasteful spending in healthcare. In alignment with national and international research priorities,[54–58] our goal is to derive a prognostic clinical prediction model that identifies children with anaphylaxis who are at heightened risk of BA. This model will address a gap in current knowledge and practice, with anticipated benefits for patient care and health system efficiency worldwide.

METHODS AND ANALYSIS:

Study Design

We will conduct a prospective multi-centre cohort study. Prospective data collection is necessary to minimize research waste in prediction modelling, accurately assess the risk and impact of BA on patients and the healthcare system, and derive a clinically useful prediction rule. Our design ensures consistency and precision of data collection of all clinically relevant potential predictors and enables accurate assessment of critical outcomes. Our methods follow established guidelines for developing clinical prediction rules.[59–68] We conform to the PROGRESS (Prognosis Research Strategy) methods of prediction modelling.[66,69–71]

Study Population

All children aged 0–17 years who present to a participating ED will be screened for study enrollment based on the following criteria:

Inclusion Criteria

1. Age < 18 years
2. Presenting to ED with an allergic reaction that matches diagnostic criteria for anaphylaxis as defined by the World Allergy Organization (WAO) in 2019.[72] *Anaphylactic reaction* is a multi-system allergic reaction characterized by one or more clinical features involving the respiratory or cardiovascular systems and associated with one or more clinical features involving the skin or gastrointestinal tract. These criteria are universally accepted and endorsed by most international allergy and emergency medicine

organizations.[15,54,73] The 2019 WAO guidelines clarify the involvement of two organ systems is not always requisite for diagnosis: "Although the diagnosis of anaphylaxis usually depends on the involvement of multiple organ systems, anaphylaxis may present as an acute cardiac or respiratory event as the only manifestation of anaphylaxis."[72] Thus, an individual with isolated hypotension, bronchospasm, or upper airway obstruction after exposure to a known or potential trigger will be deemed to have anaphylaxis, even if typical skin features are absent.[72,74]

3. Language proficiency in English or French

Exclusion Criteria

1. Anaphylactic reaction that occurred in the context of a suicidal attempt or intoxication.
2. Anaphylactic reaction that began in hospital and managed outside the ED (inpatient or outpatient unit)
3. Inability or unwillingness of individual and/or caregiver to complete the follow-up surveys post ED discharge.

Study Setting

Between April 2022 and June 2024, the study will enrol participants in EDs from seven hospitals: CHU Sainte-Justine, Children's Hospital of Eastern Ontario, Hospital for Sick Children, McMaster Children's Hospital, Children's Hospital – London Health Sciences Centre, Alberta Children's Hospital, and Stollery Children's Hospital. These EDs are members of Pediatric Emergency Research Canada (PERC; https://www.perc-canada.ca)[75]. Research staff

will follow site-specific Research Ethics Boards' (REB) guidelines for approaching potential participants and families for research studies, screening for eligibility, and obtaining consent.

Outcome

The primary outcome is development of BA. As per the recently published consensus definition,[76] to be classified as BA, an anaphylactic reaction must meet three criteria: 1) initial anaphylactic reaction followed by resolution of all initial manifestations for ≥1 hour, with no new symptoms or treatment administered in that time; 2) second phase of new or recurrent symptoms or signs that meet the consensus definition of anaphylaxis occurring within 1-48 hours from complete resolution of initial symptoms or signs; and 3) new or recurrent symptoms or signs not caused by antigen re-exposure.[35] We will capture any new or recurrent symptoms or signs, but only clinical manifestations that meet diagnostic criteria for anaphylaxis will be defined as **anaphylactic biphasic responses**. This definition focuses on *clinically important* or major biphasic reactions.[29,30] Mild symptoms that involve only the skin (e.g., urticarial rash) will be captured and classified as minor biphasic responses, but they do not meet our case definition for BA.

Data collection in ED

A research assistant (RA) or research nurse (RN) in the ED will approach potential participants to screen for eligibility and provide a study overview. When the pre-screen has been completed, the RA/RN will consult with the attending physician to confirm that the symptoms are consistent with anaphylaxis. If the attending physician considers the signs and symptoms to be more in line with another diagnosis (e.g., gastroenteritis), the patient will be excluded. After confirming

participant eligibility, the RA/RN will obtain written informed consent (and assent as appropriate) and proceed with data collection. Table 1 lists the independent variables that will be collected.

Table 1: Data collection variables

From clinical history	• Demographics: age, sex, date of birth, and self-identified race • Past medical history (e.g., cardiac disease, bronchial asthma, eczema) • Previous ED visits for anaphylaxis • Current anaphylaxis augmenting factors (e.g., physical exercise, viral illness or fever, menses in female, drugs such as non-steroidal anti-inflammatory drugs (NSAID), antacid, ß-blockers, and ACE inhibitors) • Allergen trigger (e.g., type, time of exposure and onset of symptoms, location)
From physical examination	• Participant weight • Vital signs at triage (heart rate, respiratory rate, blood pressure, and oxygen saturation) • Triage score (based on Canadian Pediatric Triage and Acuity Scale) • Physical exam findings upon arrival at ED
From pre-hospital and initial ED intervention, and disposition	• Treatment interventions (e.g., epinephrine, bronchodilators, etc.) received before arrival at ED and during transport by paramedics (if applicable) • Non-pharmacologic/supportive interventions (such as intubation and intravenous fluids) and timeline • Pharmacologic interventions (including dose, route, frequency, and time administered) • Disposition time, location (home or hospitalization), list of discharge medications, and outpatient allergy referral
From ED monitoring period	• Presence and description of new/recurrent symptoms/signs • Time of new recurring symptoms/signs • Management interventions given for biphasic reaction
From follow-up email/phone call after ED disposition	• Presence and description of new/recurrent symptoms/signs • Time of new/recurrent symptoms/signs • Management interventions given for biphasic reaction, including visits to ED/primary care providers
From 6-month follow-up (if applicable)	• If patient was seen by Allergist • If seen by Allergist, was allergic agent identified?

The RA/RN will review the physical exam findings with the clinical team (treating ED physician/bedside nurse). Because anaphylaxis is a clinical diagnosis, participants or caregivers will be asked about the spectrum of symptoms and signs experienced before and upon arrival in the ED. The RN/RA will verbally administer a structured questionnaire to participants or caregivers to collect demographics, medical history, risk factors, reaction characteristics, and symptoms. Information from the participant and from the medical record about treatment before and after ED arrival, and biphasic anaphylaxis events during the ED monitoring period, will by captured by the RN/RA. Missing data will be obtained by questioning the participant, caregiver, or treating ED team. To capture all BA events and ascertain symptom recurrence while participants are being monitored, the research RN/RA will follow the participant/caregiver throughout the ED visit. Events occurring outside study team hours will be captured in the follow-up questionnaire.

First follow-up after ED discharge or hospital admission

Published data have reported symptom recurrence up to 48 hours from anaphylaxis onset.[28,44] We will contact participants by telephone or email 2-5 days after enrollment to complete a standardized questionnaire that will capture the nature and timing of new and recurrent symptoms or signs, follow-up with health providers, return ED visits, and treatments received. Events that took place in-hospital, but were not previously captured by the study team (e.g., outside study team hours), will be verified from the participant's medical chart.

Second follow-up after ED discharge or hospital admission

Participants whose anaphylaxis trigger or culprit allergen was unknown at the time of study enrollment will be contacted 6-9 months after enrollment. We will determine if the participant had been assessed by an allergy specialist in the interim, and if so, whether an allergic agent had been identified.

Strategies for retention

For the follow-up survey, the families of participants will be asked: (1) their preferred mode of contact (email or telephone), and (2) the best time to reach them and contact number. Based on their preferences, we will send the follow-up questionnaire as an automated REDCap survey to the parent/caregiver email address or administer the survey by telephone. If the e-survey is not completed within 24 hours, a second email will be sent. If there is no response to a second email, experienced staff will contact the participant for a telephone interview. A similar schedule of repeat calls will be used to reach those who selected telephone follow-up.

Sample Size

Based on our earlier research and estimates from well-designed adult and pediatric studies,[28,35] 10% is a conservative of the population-wide event rate for BA. Our systematic reviews of potential predictors [77] and other relevant studies identified 19 potential predictive variables.[78] Recent *BMJ* and *Stat in Med* articles offer practical guidance for calculating the sample size required for the development of clinical prediction models.[79,80] Following these guidelines, we considered sample size from four perspectives, with the largest being selected as the sample size needed. The four calculations are based on: the approximate 95% confidence

interval for the overall outcome proportion 0.10 in the study population (calculated sample size needed n=139); the mean absolute prediction error of the average error in the model's outcome (n=274); achievement of an expected uniform shrinkage factor of ≤10% (n=1,529); and ensuring a small, expected optimism in the apparent proportion of overall variation explained R2 (n=719). Details of these calculations with the selection of the parameter estimates and sensitivity considerations are provided in **Supplementary Material A.** Taking the largest sample size that meets all four criteria, we need to enroll 1,529 participants with anaphylaxis. Based on previous studies by our network, we anticipate 10% loss to follow-up.[81,82] Thus, our estimated sample size is 1,682 participants.

Dependent Predictors Selection for Analysis

Table 2 lists the 19 candidate-dependent predictors that we will include in the analysis. We chose these 19 variables based on clinical studies of predictors of BA by our team and by others,[16–47] two systematic reviews,[77,83] the meta-analysis from the 2020 anaphylaxis practice parameter,[84] and clinical experience. These predictors encompass recently published BA predictors from the European Anaphylaxis Registry retrospective data.[85] Given the direct association between initially severe anaphylaxis and subsequent BA, we also include risk factors of severe anaphylaxis.[86]

Table 2: Candidate-dependent predictors that will be included in the analysis for primary objective of study, based on previous clinical studies on BA predictors

Allergen predictors	**Patient predictors**
Peanut trigger [85]	Age [34,35,38,86]
Venom trigger [86]	Male sex [86,87]
Drug trigger [11,78,84,86–89]	Previous anaphylaxis [31,36,39]
Unknown trigger [31,39,83–85]	Pre-existing asthma or chronic lung disease [26,28,42,47,86,87,89]
≥30 min from exposure to trigger to onset of symptoms [43,85]	Exercise as co-factor for anaphylaxis [1,86,90–93]
Disease predictors	**Treatment predictors**
Signs of severe anaphylaxis* [22,23,25,27,34,38,83,84,94]	Treatment of initial reaction with >1 dose of epinephrine [22,23,35,42,45,46,84,95]
Wide pulse pressure [84,95]	Treatment of initial reaction with epinephrine [34,35,44,96]
Respiratory distress or wheezing [31,35,97]	Systemic steroids [44,84]
Gastrointestinal manifestations [83,85]	Epinephrine administration >60 min from onset of reaction [20,26,35,39,98,99]
Cutaneous manifestations [69, 73]	
*Include (as defined by Brown's severity grading score)[100]: cyanosis or SpO2 ≤ 92%, hypotension, confusion, collapse, loss of consciousness, or incontinence.	

Data analysis

The statistical analysis will be performed using R statistical software version 4.0.5 (R Core Team, Vienna, Austria)[101]. Descriptive analysis will be used to summarize baseline participant demographics, anaphylaxis clinical manifestations, and management characteristics. Although race and indigenous status will be collected as demographic characteristics, we will not perform race-based analysis; these variables will be used as descriptors to demonstrate the diversity and representativeness of our sample.

Multivariable regression analysis will be used to derive a predictive model for BA. As recommended by Royston *et al.*[102], our modelling strategy will follow six steps.

1) *Evaluate data quality*. Predictors found to be complete (<10% missing data) will be used in a full model approach. Missing data will be considered Missing at Random. If any potential predictor has >10% missing value, a multiple imputation procedure will be followed to replace these values.[61,64] If >50% data are missing, the variable will be omitted from the analysis.
2) *Handle and model continuous predictors*. To maximize the predictive ability of the regression model, we will maintain continuous variables such as age.[103,104] A multivariable fractional polynomial procedure will be used to identify and model nonlinear continuous variables. Our a priori categorization of some originally continuous predictors, such as "time to epinephrine treatment," is based on plausible clinical and basic science research [77,105,106] and recent regression analysis.[39]
3) *Develop final model (predictor selection)*. Predictors that match the above two criteria will be entered in a "full model" that contains the main effects of all candidate predictors. The objective of predictors reduction is to find the best combinations of variables for accurate prediction (low mean squared error) in a model that is easy for clinicians to use and that contains as few variables as possible. Therefore, we will assess for collinearity and use shrinkage technique as a method of variable reduction.[68] Collinearity between predictors will be evaluated with correlation coefficient (r) and variance inflation factors (VIF), which measure the degree to which collinearity degrades the precision of estimate coefficients. Strongly correlated predictors ($r > 0.8$, or $VIF > 10$) will be combined in a single variable. In accordance with Harrell and Steyerberg, we will use Penalized maximum likelihood (PML)

estimation to perform shrinkage reduction (reduction of the regression coefficients to improve prediction quality). Maximizing a modified Akaike's Information Criterion will be used to choose the optimal penalty factor for PML and select the best model. This approach includes a penalty against large models to deal with the trade-off between overfitting and model simplicity.[102] The added benefit of this approach is that we could use more penalty factor if we found significant interaction.

4) *Assess model performance with three measures* [64,107,108]

   a. *Calibration* refers to the accuracy of absolute risk estimates.[107] Model calibration will be assessed by calibration slope, and graphically, by locally weighted scatterplot smoothing (LOESS) plots of observed versus predicted probabilities of the outcome. The slope of the calibration curve is a measure of over-optimism of the model predictions.

   b. *Discrimination* will be assessed by the receiver operating characteristics curve and the concordance (C) index, which measures how well the model discriminates between participants with and without BA.

   c. *Clinical usefulness* of the prediction model will be assessed using net benefit as a decision analytic.[108,109] The derived prediction rule will be cross-validated by comparing the classification of each participant with their actual primary outcome status.

5) *Validate model*

   i. *Internal validation.* Recruiting from geographically separated sites enhances generalizability and supports internal validation of the model.[61,110,111] To correct

for overfitting and quantify optimism in model performance, our model will be validated internally using bootstrapping through the following steps: [103,112,113] 1) After developing the prediction model using the entire original sample and determining apparent performance, we will generate a bootstrap sample by sampling individuals with replacement from the original sample; 2) Develop a model using the bootstrap sample (applying the same modelling and predictor selection in step 3 above); 3) Determine the apparent bootstrap performance of this model (performance of bootstrap model in the original sample and calculate the optimism as the difference between bootstrap performance and test performance); 4) Repeat steps 1 through 3 at least 500 times; and 5) Average the estimates of optimism in step 4, and subtract the value from the apparent performance obtained in step 1 to obtain an optimism-corrected estimate of performance.

ii. *External validation*: Before broad clinical implementation, our derived rule requires external validation. Lack of external validation is a limitation of many clinical prediction models.[77,114] For two reasons, this proposal focuses only on model derivation: 1) Requesting funding for external validation may be premature. Before embarking on external validation, we need proof that our *a priori* risk factors yield a clinically useful and statistically sensitive model. 2) The validation phase should be broader, in different settings, with other participants, and with different clinicians.[115,116] Our ultimate goal is to validate our model and risk score in an international setting. Such validation is feasible because PERC is a member of the Pediatric Emergency Research Networks (PERN), and member networks have a history of collaboration.[81,82,117]

6) *Present model*. As described by Sullivan *et al.*[118], we will use the regression coefficient in our final fitted model to generate a clinical decision rule that enables point-of-care risk assessment of BA. To develop a points score system, we will follow the steps described in a recent *BMJ* paper: [119] 1) Multiply and round regression coefficients of binary predictors; 2) Search for score for continuous predictors to determine the difference in regression units; 3) Estimate multiplication factor for the scores; 4) Use decision curve analysis to assign participants to risk groups and quantify any deterioration in discriminative performance; and 5) Present accompanying table of probabilities to allow points score to be translated into a predicted risk. The anticipated stoplight scoring system (green=low→discharge; yellow=moderate→monitor in ED/preference-sensitive care; red=high→admit to hospital) will inform evidence-based disposition decisions by clinicians and anticipatory guidance to families.

Patient and Public Involvement

Patients and/or the public were involved in the design and dissemination plans for this research. To promote uptake of our results, potential knowledge users have been and will be engaged throughout the project.[120] We have a multi-phase approach to maximize collaboration and opportunities for diverse knowledge users to interact at various research phases.[121] Our multi-site team includes ED clinicians as typical end-users and champions for future implementation. We have established an advisory council of external end-users (parents, youth, ED clinicians) and community partners (Food Allergy Canada, Canadian Society of Allergy & Clinical Immunology) to monitor milestones, identify potential barriers and enablers for future implementation, and guide future decision aids study. The leadership team at Food Allergy

Canada has reviewed and supports this proposal. To improve study operation and minimize the burden on patients and families, we sought feedback from the Patients and Families Advisory Committee at the Children's Hospital of Eastern Ontario Research Institute.

ETHICS AND DISSEMINATION:

Ethics

Approval will be obtained from ethics boards at all recruiting centers. Ethics approval has been received from Clinical Trials Ontario (CTO 3721) for the hospitals in Ontario. Written informed consent, and/or assent when appropriate, will be obtained from all participants or legal guardians.

The study is registered at ClinicalTrials.gov (NCT05135377). Results information from this study will be submitted to ClinicalTrials.gov.

End-of-grant KT (Knowledge Translation)

ED personnel, providers, allergists, clinical researchers, administrators, and government policy-makers can use our study outputs to improve healthcare delivery. KT will focus on informing clinicians, other key user groups, and parents and participants. Our plan has three goals: increase knowledge awareness, inform/change practice, and inform future research.[122,123]

We have a powerful infrastructure to disseminate our results. Study investigators are senior members of PERC and PERN, networks that include pediatric ED researchers worldwide (>100 hospitals across 6 PERN networks)[124], practicing clinicians, medical educators, and healthcare

administrators. PERC is closely tied to the TREKK (Translating Emergency Research Knowledge for Kids) Network of Centres of Excellence,[125] a partnership for knowledge exchange between general EDs and PERC sites. Our reporting/publication of the study results will conform to the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) checklist.[113]

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COMPETING INTERESTS STATEMENT:

All authors have read and understood BMJ policy on declaration of interests and have no relevant interest to declare. Dr Amy C. Plint is supported by a Tier I University of Ottawa Research Chair. Dr. Stephen Freedman is supported by the Alberta Children's Hospital Professorship in Child Health and Wellness.

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AUTHORS' CONTRIBUTIONS:

WA and ACP conceived the study idea. WA, ACP, and MS wrote the protocol with input from GAM, GSC, MG, JC, RZ, SS, AE, JG, CK, AD, ME, SBF, JG, NP, and MW. All authors provided input into the methodology and analysis plan. All authors approved the final protocol manuscript**.** ACP and GW are the supervisors of the study.

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SUPPLEMENTARY MATERIAL:

Supplementary Material A - Sample Size Calculation

Following (Riley 2019, Riley 2020), the sample size is considered from four perspectives, and the largest sample size calculated is selected as the overall sample size needed.

1. Approximate 95% confidence interval for overall outcome proportion in study population

$$n = \left(\frac{1.96}{\delta}\right)^2 \hat{\theta}(1-\hat{\theta})$$

$\hat{\theta} = .10$ *or* $.15$ - overall outcome proportion in study population

Then for:

$\hat{\theta} = .10$, n=139

$\hat{\theta} = .15$, n=196

2. Mean absolute prediction error (MAPE) - average error in the model's outcome

$$n = \exp\left(\frac{-0.508 + 0.259\ln(\theta) + 0.504\ln(P) - \ln(MAPE)}{0.544}\right)$$

MAPE=0.050 - suggested MAPE is no larger than 0.050 (lower values in settings may be appropriate where precise predictions are needed if consequences of wrong decisions are large)

P=18 - number of predictors

For $\hat{\theta} = .10$, then n=274

For $\hat{\theta} = .15$, then n=332

3. Achieve expected uniform shrinkage factor S

$$n = \frac{P}{(S-1)ln\left(1 - \frac{R^2_{cs}}{S}\right)}$$

R^2_{cs} =0.10 or 0.15 - proportion of overall variation

explained P=19 - number of predictors

S=0.9 or 0.85 - suggested target for shrinkage of ≤10% (i.e. S≥0.9)

For $R^2_{cs} = 0.10$, $S = 0.9$, then n=1529

For $R^2_{cs} = 0.15$, $S = 0.9$, then n=988

For $R^2_{cs} = 0.10$, $S = 0.85$, then n=959

For $R^2_{cs} = 0.15$, $S = 0.85$, then n=1529

4. Ensure a small expected optimism in apparent R^2

$$n = \frac{P}{(S-1)ln\left(1-\frac{R^2_{cs}}{S}\right)}$$

Where

$$S = \frac{R^2_{cs}}{R^2_{cs} + \delta \max\left(R^2_{cs}\right)}$$

$$\max(R^2_{cs}) = 1 - exp\left(\frac{2lnL_{null}}{n}\right)$$

$$lnL_{null} = Eln\left(\frac{E}{n}\right) + (n-E)ln\left(1-\frac{E}{n}\right)$$

and consider $\frac{E}{n} = \theta$

For $\hat{\theta} = .10$, $R^2_{cs} = 0.10$ then $\max(R^2_{cs})$ =0.48, S=0.81 and n=719

For $\hat{\theta} = .10$, $R^2_{cs} = 0.15$ then $\max(R^2_{cs})$ =0.48, S=0.81 and n=463

For $\hat{\theta} = .15$, $R^2_{cs} = 0.10$ then $\max(R^2_{cs})$ =0.57, S=0.84 and n=888

For $\hat{\theta} = .15$, $R^2_{cs} = 0.15$ then $\max(R^2_{cs})$ =0.57, S=0.84 and n=572

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	4
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	4 – 5
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	7 – 8
Objectives	3	State specific objectives, including any prespecified hypotheses	8
Methods			
Study design	4	Present key elements of study design early in the paper	9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	9 – 10
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	9 – 10
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	11
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	11 – 13
Bias	9	Describe any efforts to address potential sources of bias	N/A
Study size	10	Explain how the study size was arrived at	14 – 15
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	15 – 16
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	16 – 20
		(*b*) Describe any methods used to examine subgroups and interactions	N/A
		(*c*) Explain how missing data were addressed	17
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	N/A

Continued on next page

Results			**Page No**
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	N/A
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	N/A
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	N/A
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	N/A
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	N/A
		Cross-sectional study—Report numbers of outcome events or summary measures	N/A
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	N/A
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	N/A
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	N/A
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	N/A
Generalisability	21	Discuss the generalisability (external validity) of the study results	N/A
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	25

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Canadian Anaphylaxis Network- Predicting Recurrence after Emergency Presentation for Allergic REaction (CAN-PREPARE): A Prospective, Cohort Study Protocol

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TITLE PAGE

Title:

Canadian Anaphylaxis Network- Predicting Recurrence after Emergency Presentation for Allergic REaction (CAN-PREPARE): A Prospective, Cohort Study Protocol

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ABSTRACT:

Introduction

Anaphylaxis is a severe, potentially fatal multi-organ system manifestation of an allergic reaction. The highest incidence of anaphylaxis is in children and adolescents. Biphasic anaphylaxis (BA) is defined as the recurrence of allergic symptoms after resolution of an initial reaction. It has been reported to occur in 10-20% of cases within 1-48 hours from the onset of the initial reaction. The dilemma for physicians is determining which patients with resolved anaphylaxis should be observed for BA, and for how long. Guidelines for duration of post-anaphylaxis monitoring vary, are based on limited evidence, and can have unintended negative impacts on patient safety, quality of life, and healthcare resources. The objectives of this study are to derive a prognostic model for BA and to develop a risk-scoring system that informs disposition decisions of children who present to emergency departments (ED) with anaphylaxis.

Methods and Analysis

This prospective multi-centre cohort study will enroll 1,682 patients from seven pediatric EDs that are members of the Pediatric Emergency Research Canada network. We will enroll patients younger than 18 years of age with an allergic reaction meeting anaphylaxis diagnostic criteria. Trained ED research assistants will screen, obtain consent, and prospectively collect study data. Research assistants will follow patients during their ED visit and ascertain, in conjunction with the medical team, if the patient develops BA. A standardized follow-up survey conducted following study enrollment will determine if a biphasic reaction occurred after ED disposition. Model development will conform to the broad principles of the PROGRESS (Prognosis Research Strategy) framework and reporting will follow the TRIPOD Statement.

Ethics and Dissemination

Ethics approval has been received from all participating centres. Our dissemination plan focuses on informing clinicians, policy-makers, and parents of the results through publication in peer-reviewed journals and broadcasting on multiple media platforms.

Registration Details

ClinicalTrials.gov (NCT05135377).

Article Summary:

Strengths and limitations of this study:

1) Largest prospective cohort study on pediatric biphasic anaphylaxis conducted to-date.
2) Sample size calculation and statistical analysis plan are based on the highest methodological standard for prediction modelling research.
3) We established an international, multidisciplinary expert team encompassing pediatrics, emergency medicine, allergy/immunology, research methodology and statistics, and knowledge translation.
4) We instituted an advisory council of external parents, youth, and clinicians end-users and community partners to monitor milestones, identify potential barriers and enablers for future implementation, and guide future decision aid tools.
5) This study is not designed to generalize our findings to settings outside of an academic pediatric emergency department; this limitation may be mitigated when we yield a clinically useful and statistically sensitive model that may be externally validated.

INTRODUCTION:

Anaphylaxis is the most severe form of allergic reaction that rapidly affects multiple body systems and can be fatal.[1,2] The highest incidence is in children and adolescents.[3–8] In Canada, approximately every 10 minutes, there is an Emergency Department (ED) visit for food allergy.[9,10] Up to 80% of anaphylactic reactions in children are triggered by food,[11] and 8% of allergy-related ED visits are due to anaphylactic shock.[3]

According to the Canadian Institute for Health Information, the rate of children visiting Ontario and Alberta EDs for anaphylaxis more than doubled between 2007 and 2014.[3] Among 13- to 17-year-olds, ED visits increased significantly (from 23/100,000 in 2007 to 59/100,000 in 2014). The highest annual rate of ED visits was among children aged 4 and younger.[3] Similarly, the Cross-Canada Anaphylaxis Registry reported a steady increase in pediatric ED visits: from 1.8/1000 in 2011 to 4.5/1000 in 2015.[10,12] These estimates are higher than data from the US and Europe.[13,14]

As the volume of anaphylaxis-related ED visits continues to rise,[10,12] ambiguity in how physicians manage anaphylaxis increases the healthcare burden and may contribute to ED crowding. Current Canadian and international guidelines recommend that all patients with anaphylaxis present to the ED, and after initial reactions have been treated, remain there for a prolonged period to be monitored for biphasic anaphylaxis (BA, also called delayed or late-phase anaphylaxis).[15–17] BA is a second wave of symptoms after initial resolution.[18,19] The reported incidence of this potentially serious phenomenon varies from 10-20%; the majority occur within 1-24 hours from onset of the initial reaction.[16–47] However, these studies vary

considerably in their design (prospective vs retrospective), enrolled population (adults vs children or mixed), settings (emergency departments vs outpatient allergy clinics), and definition and severity of anaphylaxis and biphasic reaction. Recent systematic review and meta-analyses [48–50] underline these epidemiological factors that explain the significant clinical heterogeneity between previous observational studies. This inconsistency of the literature creates dilemma for ED physicians in deciding which patients should be observed and the optimum duration of observation.[51] As a result, guidelines for post-anaphylaxis care vary,[1,16,17] are based on poor or little evidence, and have negative impacts on patient safety and quality of life.[18,36,52,53] This clinical uncertainty originates from the lack of validated clinical predictors for BA. Consequently, many children are hospitalized or undergo prolonged monitoring in the ED after resolution of initial anaphylaxis.[53,54]

In the United States, ED care and hospitalizations are the largest drivers of annual direct medical costs ($1.9 billion) for food allergic children.[55] The incremental cost of extended ED observation of resolved anaphylaxis (6 hours versus 1 hour) is $62,374 USD per case of BA identified ($68,411 USD from the societal perspective). ED monitoring beyond 6 hours of patients who quickly stabilize after treatment is associated with an incremental cost-effectiveness ratio of $230,202 per case observed (societal perspective).[56] As ED crowding and visits for anaphylaxis increase, current post-anaphylaxis clinical practice is neither sustainable nor cost-effective.[29]

Providing the best evidence-based value care at the lowest cost is critical to optimize resource stewardship and eliminate wasteful spending in healthcare. In alignment with national and

international research priorities,[57–61] our goal is to derive a prognostic clinical prediction model that identifies children with anaphylaxis who are at heightened risk of BA. This model will address a gap in current knowledge and practice, with anticipated benefits for patient care and health system efficiency worldwide.

METHODS AND ANALYSIS:

Study Design

We will conduct a prospective multi-centre cohort study. Prospective data collection is necessary to minimize research waste in prediction modelling, accurately assess the risk and impact of BA on patients and the healthcare system, and derive a clinically useful prediction rule. Our design ensures consistency and precision of data collection of all clinically relevant potential predictors and enables accurate assessment of critical outcomes. Our methods follow established guidelines for developing clinical prediction rules.[62–71] We conform to the PROGRESS (Prognosis Research Strategy) methods of prediction modelling.[69,72–74]

Study Population

All children aged 0–17 years who present to a participating ED will be screened for study enrollment based on the following criteria:

Inclusion Criteria

1. Age < 18 years

2. Presenting to ED with an allergic reaction that matches diagnostic criteria for anaphylaxis as defined by the World Allergy Organization (WAO) in 2019.[75] *Anaphylactic reaction* is a multi-system allergic reaction characterized by one or more clinical features involving the respiratory or cardiovascular systems and associated with one or more clinical features involving the skin or gastrointestinal tract. These criteria are universally accepted and endorsed by most international allergy and emergency medicine organizations.[15,57,76] The 2019 WAO guidelines clarify the involvement of two organ systems is not always requisite for diagnosis: "Although the diagnosis of anaphylaxis usually depends on the involvement of multiple organ systems, anaphylaxis may present as an acute cardiac or respiratory event as the only manifestation of anaphylaxis."[75] Thus, an individual with isolated hypotension, bronchospasm, or upper airway obstruction after exposure to a known or potential trigger will be deemed to have anaphylaxis, even if typical skin features are absent.[75,77]
3. Language proficiency in English or French

Exclusion Criteria

1. Anaphylactic reaction that occurred in the context of a suicidal attempt or intoxication.
2. Anaphylactic reaction that began in hospital and managed outside the ED (inpatient or outpatient unit)
3. Inability or unwillingness of individual and/or caregiver to complete the follow-up surveys post ED discharge.

Study Setting

Between April 2022 and June 2024, the study will enrol participants in EDs from seven hospitals: CHU Sainte-Justine, Children's Hospital of Eastern Ontario, Hospital for Sick Children, McMaster Children's Hospital, Children's Hospital – London Health Sciences Centre, Alberta Children's Hospital, and Stollery Children's Hospital. These EDs are members of Pediatric Emergency Research Canada (PERC; https://www.perc-canada.ca)[78]. Research staff will follow site-specific Research Ethics Boards' (REB) guidelines for approaching potential participants and families for research studies, screening for eligibility, and obtaining consent.

Outcome

The primary outcome is development of BA. As per the recently published consensus definition,[79] to be classified as BA, an anaphylactic reaction must meet three criteria: 1) initial anaphylactic reaction followed by resolution of all initial manifestations for ≥1 hour, with no new symptoms or treatment administered in that time; 2) second phase of new or recurrent symptoms or signs that meet the consensus definition of anaphylaxis occurring within 1-48 hours from complete resolution of initial symptoms or signs; and 3) new or recurrent symptoms or signs not caused by antigen re-exposure.[35] We will capture any new or recurrent symptoms or signs, but only clinical manifestations that meet diagnostic criteria for anaphylaxis will be defined as **anaphylactic biphasic responses**. This definition focuses on *clinically important* or major biphasic reactions.[29,30] Mild symptoms that involve only the skin (e.g., urticarial rash) will be captured and classified as minor biphasic responses, but they do not meet our case definition for BA.

Data collection in ED

A research assistant (RA) or research nurse (RN) in the ED will approach potential participants to screen for eligibility and provide a study overview. When the pre-screen has been completed, the RA/RN will consult with the attending physician to confirm that the symptoms are consistent with anaphylaxis. If the attending physician considers the signs and symptoms to be more in line with another diagnosis (e.g., gastroenteritis), the patient will be excluded. After confirming participant eligibility, the RA/RN will obtain written informed consent (and assent as appropriate) and proceed with data collection. Table 1 lists the independent variables that will be collected.

Table 1: Data collection variables

From clinical history	• Demographics: age, sex, date of birth, and self-identified race • Past medical history (e.g., cardiac disease, bronchial asthma, eczema) • Previous ED visits for anaphylaxis • Current anaphylaxis augmenting factors (e.g., physical exercise, viral illness or fever, menses in female, drugs such as non-steroidal anti-inflammatory drugs (NSAID), antacid, ß-blockers, and ACE inhibitors) • Allergen trigger (e.g., type, time of exposure and onset of symptoms, location)
From physical examination	• Participant weight • Vital signs at triage (heart rate, respiratory rate, blood pressure, and oxygen saturation) • Triage score (based on Canadian Pediatric Triage and Acuity Scale) • Physical exam findings upon arrival at ED
From pre-hospital and initial ED intervention, and disposition	• Treatment interventions (e.g., epinephrine, bronchodilators, etc.) received before arrival at ED and during transport by paramedics (if applicable) • Non-pharmacologic/supportive interventions (such as intubation and intravenous fluids) and timeline • Pharmacologic interventions (including dose, route, frequency, and time administered) • Disposition time, location (home or hospitalization), list of discharge medications, and outpatient allergy referral
From ED monitoring	• Presence and description of new/recurrent

period	symptoms/signs • Time of new recurring symptoms/signs • Management interventions given for biphasic reaction
From follow-up email/phone call after ED disposition	• Presence and description of new/recurrent symptoms/signs • Time of new/recurrent symptoms/signs • Management interventions given for biphasic reaction, including visits to ED/primary care providers
From 6-month follow-up (if applicable)	• If patient was seen by Allergist • If seen by Allergist, was allergic agent identified?

The RA/RN will review the physical exam findings with the clinical team (treating ED physician/bedside nurse). Because anaphylaxis is a clinical diagnosis, participants or caregivers will be asked about the spectrum of symptoms and signs experienced before and upon arrival in the ED. The RN/RA will verbally administer a structured questionnaire to participants or caregivers to collect demographics, medical history, risk factors, reaction characteristics, and symptoms. Information from the participant and from the medical record about treatment before and after ED arrival, and biphasic anaphylaxis events during the ED monitoring period, will by captured by the RN/RA. Missing data will be obtained by questioning the participant, caregiver, or treating ED team. To capture all BA events and ascertain symptom recurrence while participants are being monitored, the research RN/RA will follow the participant/caregiver throughout the ED visit. Events occurring outside study team hours will be captured in the follow-up questionnaire.

First follow-up after ED discharge or hospital admission

Published data have reported symptom recurrence up to 48 hours from anaphylaxis onset.[28,44] We will contact participants by telephone or email 2-5 days after enrollment to complete a standardized questionnaire that will capture the nature and timing of new and recurrent

symptoms or signs, follow-up with health providers, return ED visits, and treatments received. Events that took place in-hospital, but were not previously captured by the study team (e.g., outside study team hours), will be verified from the participant's medical chart.

Second follow-up after ED discharge or hospital admission

Participants whose anaphylaxis trigger or culprit allergen was unknown at the time of study enrollment will be contacted 6-9 months after enrollment. We will determine if the participant had been assessed by an allergy specialist in the interim, and if so, whether an allergic agent had been identified.

Strategies for retention

For the follow-up survey, the families of participants will be asked: (1) their preferred mode of contact (email or telephone), and (2) the best time to reach them and contact number. Based on their preferences, we will send the follow-up questionnaire as an automated REDCap survey to the parent/caregiver email address or administer the survey by telephone. If the e-survey is not completed within 24 hours, a second email will be sent. If there is no response to a second email, experienced staff will contact the participant for a telephone interview. A similar schedule of repeat calls will be used to reach those who selected telephone follow-up.

Sample Size

Based on our research[35,48,49], estimates from prospective ED studies [28,44,45,96] and published data from large adult and pediatric studies,[80,81] 10% is a conservative estimate of the population-wide event rate of BA. Our systematic reviews of potential predictors [48] and

other relevant studies identified 19 potential predictive variables.[82] Recent *BMJ* and *Stat in Med* articles offer practical guidance for calculating the sample size required for the development of clinical prediction models.[83,84] Following these guidelines, we considered sample size from four perspectives, with the largest being selected as the sample size needed. The four calculations are based on: the approximate 95% confidence interval for the overall outcome proportion 0.10 in the study population (calculated sample size needed n=139); the mean absolute prediction error of the average error in the model's outcome (n=274); achievement of an expected uniform shrinkage factor of ≤10% (n=1,529); and ensuring a small, expected optimism in the apparent proportion of overall variation explained R2 (n=719). Details of these calculations with the selection of the parameter estimates and sensitivity considerations are provided in **Supplementary Material A.** Taking the largest sample size that meets all four criteria, we need to enroll 1,529 participants with anaphylaxis. Based on previous studies by our network, we anticipate 10% loss to follow-up.[85,86] Thus, our estimated sample size is 1,682 participants.

Dependent Predictors Selection for Analysis

Table 2 lists the 19 candidate-dependent predictors that we will include in the analysis. We chose these 19 variables based on clinical studies of predictors of BA by our team and by others,[16–47] two systematic reviews,[48,50] the meta-analysis from the 2020 anaphylaxis practice parameter,[49] and clinical experience. These predictors encompass recently published BA predictors from the European Anaphylaxis Registry retrospective data.[87] Given the direct association between initially severe anaphylaxis and subsequent BA, we also include risk factors of severe anaphylaxis.[88]

Table 2: Candidate-dependent predictors that will be included in the analysis for primary objective of study, based on previous clinical studies on BA predictors

Allergen predictors	**Patient predictors**
Peanut trigger [87]	Age [34,35,38,88]
Venom trigger [88]	Male sex [88,89]
Drug trigger [11,49,88–92]	Previous anaphylaxis [31,36,39]
Unknown trigger [31,39,49,50,87]	Pre-existing asthma or chronic lung disease [26,28,42,47,88,89,91]
≥30 min from exposure to trigger to onset of symptoms [43,87]	Exercise as co-factor for anaphylaxis [1,88,93–96]
Disease predictors	**Treatment predictors**
Signs of severe anaphylaxis* [22,23,25,27,34,38,49,50,97]	Treatment of initial reaction with >1 dose of epinephrine [22,23,35,42,45,46,49,98]
Wide pulse pressure [49,98]	Treatment of initial reaction with epinephrine [34,35,44,99]
Respiratory distress or wheezing [31,35,100]	Systemic steroids [44,49]
Gastrointestinal manifestations [50,87]	Epinephrine administration >60 min from onset of reaction [20,26,35,39,101,102]
Cutaneous manifestations [69, 73]	
*Include (as defined by Brown's severity grading score)[103]: cyanosis or SpO2 ≤ 92%, hypotension, confusion, collapse, loss of consciousness, or incontinence.	

Data analysis

The statistical analysis will be performed using R statistical software version 4.0.5 (R Core Team, Vienna, Austria)[104]. Descriptive analysis will be used to summarize baseline participant demographics, anaphylaxis clinical manifestations, and management characteristics. Although race and indigenous status will be collected as demographic characteristics, we will not perform race-based analysis; these variables will be used as descriptors to demonstrate the diversity and representativeness of our sample.

Multivariable regression analysis will be used to derive a predictive model for BA. As recommended by Royston *et al.*[105], our modelling strategy will follow six steps.

1) *Evaluate data quality*. Predictors found to be complete (<10% missing data) will be used in a full model approach. Missing data will be considered Missing at Random. If any potential predictor has >10% missing value, a multiple imputation procedure will be followed to replace these values.[64,67] If >50% data are missing, the variable will be omitted from the analysis.
2) *Handle and model continuous predictors*. To maximize the predictive ability of the regression model, we will maintain continuous variables such as age.[106,107] A multivariable fractional polynomial procedure will be used to identify and model nonlinear continuous variables. Our a priori categorization of some originally continuous predictors, such as "time to epinephrine treatment," is based on plausible clinical and basic science research [48,108,109] and recent regression analysis.[39]
3) *Develop final model (predictor selection)*. Predictors that match the above two criteria will be entered in a "full model" that contains the main effects of all candidate predictors. The objective of predictors reduction is to find the best combinations of variables for accurate prediction (low mean squared error) in a model that is easy for clinicians to use and that contains as few variables as possible. Therefore, we will assess for collinearity and use shrinkage technique as a method of variable reduction.[71] Collinearity between predictors will be evaluated with correlation coefficient (r) and variance inflation factors (VIF), which measure the degree to which collinearity degrades the precision of estimate coefficients. Strongly correlated predictors ($r > 0.8$, or $VIF > 10$) will be combined in a single variable. In accordance with Harrell and Steyerberg, we will use Penalized maximum likelihood (PML)

estimation to perform shrinkage reduction (reduction of the regression coefficients to improve prediction quality). Maximizing a modified Akaike's Information Criterion will be used to choose the optimal penalty factor for PML and select the best model. This approach includes a penalty against large models to deal with the trade-off between overfitting and model simplicity.[105] The added benefit of this approach is that we could use more penalty factor if we found significant interaction.

4) *Assess model performance with three measures* [67,110,111]

   a. *Calibration* refers to the accuracy of absolute risk estimates.[110] Model calibration will be assessed by calibration slope, and graphically, by locally weighted scatterplot smoothing (LOESS) plots of observed versus predicted probabilities of the outcome. The slope of the calibration curve is a measure of over-optimism of the model predictions.

   b. *Discrimination* will be assessed by the receiver operating characteristics curve and the concordance (C) index, which measures how well the model discriminates between participants with and without BA.

   c. *Clinical usefulness* of the prediction model will be assessed using net benefit as a decision analytic.[111,112] The derived prediction rule will be cross-validated by comparing the classification of each participant with their actual primary outcome status.

5) *Validate model*

   i. *Internal validation.* Recruiting from geographically separated sites enhances generalizability and supports internal validation of the model.[64,113,114] To correct

for overfitting and quantify optimism in model performance, our model will be validated internally using bootstrapping through the following steps: [106,115,116] 1) After developing the prediction model using the entire original sample and determining apparent performance, we will generate a bootstrap sample by sampling individuals with replacement from the original sample; 2) Develop a model using the bootstrap sample (applying the same modelling and predictor selection in step 3 above); 3) Determine the apparent bootstrap performance of this model (performance of bootstrap model in the original sample and calculate the optimism as the difference between bootstrap performance and test performance); 4) Repeat steps 1 through 3 at least 500 times; and 5) Average the estimates of optimism in step 4, and subtract the value from the apparent performance obtained in step 1 to obtain an optimism-corrected estimate of performance.

ii. *External validation*: Before broad clinical implementation, our derived rule requires external validation. Lack of external validation is a limitation of many clinical prediction models.[48,117] For two reasons, this proposal focuses only on model derivation: 1) Requesting funding for external validation may be premature. Before embarking on external validation, we need proof that our *a priori* risk factors yield a clinically useful and statistically sensitive model. 2) The validation phase should be broader, in different settings, with other participants, and with different clinicians.[118,119] Our ultimate goal is to validate our model and risk score in an international setting. Such validation is feasible because PERC is a member of the Pediatric Emergency Research Networks (PERN), and member networks have a history of collaboration.[85,86,120]

6) *Present model*. As described by Sullivan *et al.*[121], we will use the regression coefficient in our final fitted model to generate a clinical decision rule that enables point-of-care risk assessment of BA. To develop a points score system, we will follow the steps described in a recent *BMJ* paper: [122] 1) Multiply and round regression coefficients of binary predictors; 2) Search for score for continuous predictors to determine the difference in regression units; 3) Estimate multiplication factor for the scores; 4) Use decision curve analysis to assign participants to risk groups and quantify any deterioration in discriminative performance; and 5) Present accompanying table of probabilities to allow points score to be translated into a predicted risk. The anticipated stoplight scoring system (green=low→discharge; yellow=moderate→monitor in ED/preference-sensitive care; red=high→admit to hospital) will inform evidence-based disposition decisions by clinicians and anticipatory guidance to families.

Patient and Public Involvement

Patients and/or the public were involved in the design and dissemination plans for this research. To promote uptake of our results, potential knowledge users have been and will be engaged throughout the project.[123] We have a multi-phase approach to maximize collaboration and opportunities for diverse knowledge users to interact at various research phases.[124] Our multi-site team includes ED clinicians as typical end-users and champions for future implementation. We have established an advisory council of external end-users (parents, youth, ED clinicians) and community partners (Food Allergy Canada, Canadian Society of Allergy & Clinical Immunology) to monitor milestones, identify potential barriers and enablers for future implementation, and guide future decision aids study. The leadership team at Food Allergy

Canada has reviewed and supports this proposal. To improve study operation and minimize the burden on patients and families, we sought feedback from the Patients and Families Advisory Committee at the Children's Hospital of Eastern Ontario Research Institute.

ETHICS AND DISSEMINATION:

Ethics

Ethics approval has been received from all recruiting centers Written informed consent, and/or assent when appropriate, will be obtained from all participants or legal guardians.

The study is registered at ClinicalTrials.gov (NCT05135377). Results information from this study will be submitted to ClinicalTrials.gov.

End-of-grant KT (Knowledge Translation)

ED personnel, providers, allergists, clinical researchers, administrators, and government policy-makers can use our study outputs to improve healthcare delivery. KT will focus on informing clinicians, other key user groups, and parents and participants. Our plan has three goals: increase knowledge awareness, inform/change practice, and inform future research.[125,126]

We have a powerful infrastructure to disseminate our results. Study investigators are senior members of PERC and PERN, networks that include pediatric ED researchers worldwide (>100 hospitals across 6 PERN networks)[127], practicing clinicians, medical educators, and healthcare administrators. PERC is closely tied to the TREKK (Translating Emergency Research

Knowledge for Kids) Network of Centres of Excellence,[128] a partnership for knowledge exchange between general EDs and PERC sites. Our reporting/publication of the study results will conform to the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) checklist.[116]

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COMPETING INTERESTS STATEMENT:

All authors have read and understood BMJ policy on declaration of interests and have no relevant interest to declare. Dr Amy C. Plint is supported by a Tier I University of Ottawa Research Chair. Dr. Stephen Freedman is supported by the Alberta Children's Hospital Professorship in Child Health and Wellness.

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AUTHORS' CONTRIBUTIONS:

WA and ACP conceived the study idea. WA, ACP, and MS wrote the protocol with input from GAM, GSC, MG, JC, RZ, SS, AE, JG, CK, AD, ME, SBF, JG, NP, and MW. All authors provided input into the methodology and analysis plan. All authors approved the final protocol manuscript**.** ACP and GW are the supervisors of the study.

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SUPPLEMENTARY MATERIAL:

Supplementary Material A - Sample Size Calculation

Following (Riley 2019, Riley 2020), the sample size is considered from four perspectives, and the largest sample size calculated is selected as the overall sample size needed.

1. Approximate 95% confidence interval for overall outcome proportion in study population

$$n = \left(\frac{1.96}{\delta}\right)^2 \hat{\theta}(1-\hat{\theta})$$

$\hat{\theta} = .10$ *or* $.15$ - overall outcome proportion in study population

Then for:

$\hat{\theta} = .10$, n=139

$\hat{\theta} = .15$, n=196

2. Mean absolute prediction error (MAPE) - average error in the model's outcome

$$n = \exp\left(\frac{-0.508 + 0.259\ln(\theta) + 0.504\ln(P) - \ln(MAPE)}{0.544}\right)$$

MAPE=0.050 - suggested MAPE is no larger than 0.050 (lower values in settings may be appropriate where precise predictions are needed if consequences of wrong decisions are large)

P=18 - number of predictors

For $\hat{\theta} = .10$, then n=274

For $\hat{\theta} = .15$, then n=332

3. Achieve expected uniform shrinkage factor S

$$n = \frac{P}{(S-1)ln\left(1 - \frac{R^2_{cs}}{S}\right)}$$

R^2_{cs} =0.10 or 0.15 - proportion of overall variation

explained P=19 - number of predictors

S=0.9 or 0.85 - suggested target for shrinkage of ≤10% (i.e. S≥0.9)

For $R^2_{cs} = 0.10,\ S = 0.9$, then n=1529

For $R^2_{cs} = 0.15,\ S = 0.9$, then n=988

For $R^2_{cs} = 0.10,\ S = 0.85$, then n=959

For $R^2_{cs} = 0.15,\ S = 0.85$, then n=1529

4. Ensure a small expected optimism in apparent R^2

$$n = \frac{P}{(S-1)ln\left(1-\frac{R^2_{cs}}{S}\right)}$$

Where

$$S = \frac{R^2_{cs}}{R^2_{cs} + \delta \max\left(R^2_{cs}\right)}$$

$$\max(R^2_{cs}) = 1 - exp\left(\frac{2lnL_{null}}{n}\right)$$

$$lnL_{null} = Eln\left(\frac{E}{n}\right) + (n-E)ln\left(1-\frac{E}{n}\right)$$

and consider $\frac{E}{n} = \theta$

For $\hat{\theta} = .10,\ R^2_{cs} = 0.10$ then $\max(R^2_{cs})$ =0.48, S=0.81 and n=719

For $\hat{\theta} = .10,\ R^2_{cs} = 0.15$ then $\max(R^2_{cs})$ =0.48, S=0.81 and n=463

For $\hat{\theta} = .15,\ R^2_{cs} = 0.10$ then $\max(R^2_{cs})$ =0.57, S=0.84 and n=888

For $\hat{\theta} = .15,\ R^2_{cs} = 0.15$ then $\max(R^2_{cs})$ =0.57, S=0.84 and n=572

References

Riley RD et al, Calculating the sample size required for developing a clinical prediction model. *BMJ* 2020;368:m441 doi: 10.1136/bmj.m441.

Riley RD, Snell KI, Ensor J, etal . Minimum sample size for developing a multivariable prediction model: PART II - binary and time-to-event outcomes. *Stat Med* 2019;38:1276-96. 10.1002/sim.7992 30357870

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	4
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	4 – 5
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	7 – 8
Objectives	3	State specific objectives, including any prespecified hypotheses	8
Methods			
Study design	4	Present key elements of study design early in the paper	9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	9 – 10
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	9 – 10
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	11
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	11 – 13
Bias	9	Describe any efforts to address potential sources of bias	N/A
Study size	10	Explain how the study size was arrived at	14 – 15
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	15 – 16
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	16 – 20
		(*b*) Describe any methods used to examine subgroups and interactions	N/A
		(*c*) Explain how missing data were addressed	17
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	N/A

Continued on next page

Results			**Page No**
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	N/A
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	N/A
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	N/A
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	N/A
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	N/A
		Cross-sectional study—Report numbers of outcome events or summary measures	N/A
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	N/A
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	N/A
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	N/A
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	N/A
Generalisability	21	Discuss the generalisability (external validity) of the study results	N/A
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	25

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.