Investigating Novel Predictions of Hypoglycemia Occurrence Using Real-World Models (iNPHORM Study): A Study Protocol

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INTRODUCTION	RESEARCH QUESTION	OBJECTIVES
- There exists a pressing need for validated, pragmatic methods that elucidate the profile of subgroups most affected by iatrogenic hypoglycemia in the real world (RW). - To address this gap, our research team designed the iNPHORM study: a nationwide, longitudinal assessment of the RW distribution and stratified risk of diabetes-related hypoglycemia.	Among American adults with type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) at-risk of iatrogenic hypoglycemia, 1) what is the real-world frequency of hypoglycemia; and 2) who is at greatest risk of experiencing hypoglycemia and why?	- To quantify the RW incidence of daytime and nocturnal severe hypoglycemia (SH) and non-severe hypoglycemia in adults with T1DM and T2DM taking insulin and/or secretagogues. - To develop and validate RW risk prediction models for SH, non-severe daytime hypoglycemia (NSDH), and non-severe nocturnal hypoglycemia (NSNH).

STUDY DESIGN & SAMPLE

Study Design

- Ambidirectional observational cohort design

Participant Sampling Strategy

SOURCE POPULATION

- Participants will be recruited from a representative online panel of the general public (USA) with diabetes managed by Ipsos.
- Ipsos Universe: n≈10,000 T1DM; n≈58,000 T2DM

ELIGIBILITY CRITERIA

Eligible/consenting individuals will be conveniently sampled.

Inclusion	Exclusion
- Adults (≥18 to <90 years old) - Self-reported T1DM or T2DM - Use of insulin and/or secretagogues for ≥1 year at the time of enrolment - Living in the USA for ≥1 year at the time of enrolment	- Unable to understand and read English - Currently pregnant or pregnant within the previous year - Currently participating in a diabetes drug research trial

QUOTA SAMPLING STRATEGY

T2DM (≤90%)

Male/
Female:
≥10%

≥75 y.o.:
≥5%

Insulin (no secretagogues)
≥ 10%

Secretagogues (no insulin)
≥ 10%

Insulin + Secretagogues
≥ 10%

T1DM (≥10%)

Insulin
100%

TARGET SAMPLE

- A total of n=1,250 individuals will be targeted.
- Eligible/consenting individuals will be required to complete a baseline questionnaire prior to study enrollment.
- A one-time replacement will occur to maximize retention.

DATA COLLECTION & PLANNED ANALYSES

Data Collection & Outcome Measures

- Data will be collected online (via multiple e-formats) using pretested self-administered, self-reported questionnaires (**Table 1**) disseminated at baseline and on a monthly basis for 12 months (**Fig 1**).
- Emailed touch-points and honoraria will be used to promote retention.

Baseline Questionnaire

- NSDH (past 30 days), NSNH (past 30 days), SH (past year)
- Socio-demographic characteristics
- Clinical characteristics (e.g., therapies, healthcare, comorbidities)
- Psychosocial/behavioural traits

Monthly Follow-up Questionnaire

- NSDH (past 30 days), NSNH (past 30 days), and SH (since the last FQ)
- Any changes in clinical traits (e.g., therapies, A1C, complications)

InHypo-DM Person with Diabetes Questionnaire¹

Modifiable factors that influence hypoglycemia self-management

Hypoglycemia Fear Survey II²

Validated 33-item survey

Table 1. iNPHORM questionnaires

Fig 1. Questionnaire dissemination

Planned Statistical Analyses

- Incidence proportions and densities for SH, NSDH, and NSNH will be described at baseline and throughout the follow-up period.
- Logistic regression will be used to develop and validate prediction models for SH, NSDH, and NSNH based on traditional and novel risk factors.
- Risk scores will be devised and translated into formats accessible within RW practice (i.e., score charts and nomograms).

SIGNIFICANCE

- The iNPHORM Study is one of few prospective RW investigations of hypoglycemia quantification and risk stratification in people with diabetes.
- Self-reported and self-administered questionnaires offer a mechanism for obtaining valid RW hypoglycemia data, overcoming many of the limitations associated with alternative data capture strategies.
- The results of the iNPHORM Study may lead to improvements in RW hypoglycemia detection and interventional effectiveness.