FLUIDX
MEDICAL TECHNOLOGY

Statistical Analysis Plan

Evaluation of a Simple-prep Controlled Embolic (GPX Trial)

[redacted]

[redacted]

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Approvals

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1. Introduction

The purpose of this statistical analysis plan (SAP) is to outline the data handling methods and planned analyses to be used for the Fluidx GPX Trial. Additional analyses of the study data beyond the analyses pre-specified in this plan are expected, and therefore the SAP does not preclude *ad hoc* analyses that may provide additional useful information on the study device.

2. Abbreviations & Definitions

AE	Adverse event
CEC	Clinical events committee
FAS	Full analysis set
FDA	Food and Drug Administration (U.S.)
ICH	International Conference on Harmonization
MAE	Major adverse event
MedDRA	Medical Dictionary for Regulatory Activities
QI	Quality improvement
SAP	Statistical analysis plan
SAS	Statistical analysis system

3. Study Design

The study is a is a single-arm, open label, non-randomized, prospective, multicenter, multinational pivotal trial.

4. Randomization and Blinding

The study is non-randomized and no blinding to treatment of the subject or attending physician is intended.

5. Analysis Populations

The primary analysis will consist of all available data on all subjects enrolled, referred to in *ICH E9 Statistical Principles for Clinical Trials* as the "full analysis set." As the study is a treatment-only, single arm design, comparisons between treatment and control groups are not pertinent, and summaries of results will principally be presented for the entire study population.

6. Study Endpoints

The primary effectiveness endpoint directly measures successful embolization of the target vessel, consistent with quality improvement (QI) standards published by the Society of Interventional

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Radiology (Dariushnia; Angle). The Dariushnia 2021 QI standards article provides a general definition of success (i.e., "... defined broadly as the immediate angiography result and is typically evaluated with completion angiography"). The definition for the present study is conservatively set to require occlusion such that no clinically significant contrast enhancement is seen.

The primary safety endpoint includes events of specific interest in embolization procedures, defined in agreement with FDA, and is, therefore, an appropriate metric to assess the safety of the embolization device.

Effectiveness is assessed immediately post-procedure, and follow-up of 30 days represents a realistic test of an embolic device, with sufficient time to identify and assess risks.

6.1. Primary Effectiveness Endpoint

The primary effectiveness endpoint for the study is delivery of the GPX Embolic Device to the target vessel embolization site(s) determined by the investigator at the time of enrollment, and successful occlusion of flow immediately beyond the target vessel embolization site(s), as determined by the core lab via comparison of the pre- and final post-embolization images.

6.2. Primary Safety Endpoint

The primary safety endpoint for the study is freedom from major adverse events (MAEs) through 30 days post-index procedure. MAEs are defined as device-related serious adverse events, as adjudicated by the Clinical Events Committee (CEC), comprising the following types:

- Nontarget embolization with ischemia in an unintended anatomical area
- Systemic allergic and/or toxic reaction to the GPX Embolic Device
- Catheter entrapment and/or breakage
- Culture-proven abscess in target organ/tissue
- Embolization-related death

6.3. Secondary Endpoints

The secondary endpoints for the study are the occurrence of:

- Device-related adverse events (AE) through 30 days post-index procedure
- Adjunctive embolization agent usage during the embolization procedure
- Catheter occlusion due to the GPX Embolic Material

7. General Statistical Considerations

The following general comments apply to all statistical analyses and data presentations.

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7.1. Descriptive Statistics

Continuous data will be summarized using descriptive statistics: n, mean, standard deviation, standard error, median, and range or interquartile range. Discrete variables will be summarized using frequency counts and percentages. For ordinal-scaled variables, a combination of the above may be employed as appropriate: frequency and percentage of observations within a category and means and standard deviations of the scores of the categories. For events that can occur more than once in a single subject, such as adverse events (AEs), the percentage will be based on the number of subjects experiencing the event; both subject and event counts will be reported.

7.2. Significance level

Tests of hypotheses against performance goals (e.g., the primary endpoints) will be performed using one-sided tests at an overall alpha level of 0.025. Other statistical testing, including ad hoc tests not specified in this document, will be performed using two-sided hypothesis tests at an overall alpha level of 0.05. The results of any ad hoc statistical test not prespecified in the protocol and SAP will not be presented in the labelling of the investigational device.

7.3. Duration Variables

Study Day 0 is the day of study device deployment (index procedure). Study day is calculated relative to day 0 and will appear in the listings where applicable:

Study Day = (Date of Event – Date of Study Device Deployment)

Duration variables will be calculated using the general formula:

[(end date – start date)]

7.4. Missing Data

As stated above, the primary analysis of all endpoints will be conducted on the full analysis set (FAS), and every effort will be made to retain subjects for the intended length of follow-up to minimize the incidence of missingness. For the primary endpoints, methods for replacing missing data such as last value carried forward or multiple imputation will not be routinely used; however, sensitivity analyses incorporating imputation will be performed for the primary endpoints including a tipping point analysis.

For the primary safety endpoint, a tipping point analysis will be performed to evaluate the impact of missing data on study conclusion. Every combination of best/worst case values will be imputed to examine under what circumstances the results change. The best/worst case values used for the primary safety endpoint will be the binary success and failure of this endpoint.

In addition, for the primary effectiveness endpoint, a tipping point analysis will be performed to evaluate the impact of missing data on study conclusion. Every combination of best/worst case values will be imputed to examine under what circumstances the results change. The best/worst

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case values used for the primary effectiveness endpoint will be the binary success and failure of this endpoint.

7.5. Software

All statistical analyses will be performed using Statistical Analysis System (SAS) for Windows (version 9.4 or higher, SAS Institute Inc. Cary, NC) or R (version 3.2 or higher, R Foundation for Statistical Computing, Vienna, Austria) or other widely available statistical or graphical software.

8. General Statistical Summaries

8.1. Subject Disposition

Subject accountability and study discontinuation will be summarized. Subject accountability at each visit will be summarized as the number of subjects with complete visits, missed visits, or study discontinuations prior to the visit. All subjects who do not complete the study will be tabulated by reason for discontinuation.

8.2. Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized, including at a minimum age, sex at birth, race, and ethnicity.

8.3. Medical History

Medical history will be summarized, including but not limited to the subject's history of anemia, chronic kidney disease, coronary artery disease, diabetes mellitus, hypertension requiring treatment, immunosuppression, liver disease, peripheral vascular disease, and tobacco use.

8.4. Adverse Events

Summary tables and listings will be provided for all reported adverse events, which will additionally be reported by seriousness and relatedness. Such summaries will comprise the number and percentage of subjects with an adverse event and the total number of such events. The proportion of subjects with events will be considered primary for analysis of adverse events.

AEs will additionally be classified according to the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. Multiple occurrences of the same AE are counted once at the maximum grade and strongest relationship, as appropriate. Adverse events adjudicated by the CEC as *definitely* or *probably* device-related will be considered related adverse events for data analytic purposes. Events adjudicated by the CEC as *possibly*, *unlikely,* or *not related* will not be considered device-related adverse events for data analytic purposes.

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9. Analysis of Study Endpoints

9.1. Primary Effectiveness Endpoint

The primary effectiveness endpoint will be tested against a predefined performance goal as developed and stated in the study protocol using Clopper-Pearson (exact) tests of a single binomial proportion against a fixed null hypothesis.

Formally, the hypotheses to be tested for the primary effectiveness endpoint are as follows:

H0: $r_E \leq 0.87$

HA: $r_E > 0.87$,

where r_E is the proportion of subjects experiencing effectiveness success and 0.87 is the corresponding performance goal.

The hypotheses above will be tested at a one-sided alpha level of 0.025 and endpoint success will be declared if the performance goal is met (i.e., if the null hypothesis is rejected in favor of the alternative hypothesis).

9.2. Primary Safety Endpoint

The primary safety endpoint will be tested against a predefined performance goal as developed and stated in the study protocol using Clopper-Pearson (exact) tests of a single binomial proportion against a fixed null hypothesis.

Formally, the hypotheses to be tested for the primary safety endpoint are as follows:

H0: $r_S \geq 0.13$

HA: $r_S < 0.13$,

where r_S is the proportion of subjects experiencing a primary safety event and 0.13 is the corresponding performance goal.

The hypotheses above will be tested at a one-sided alpha level of 0.025 and endpoint success will be declared if the performance goal is met (i.e., if the null hypothesis is rejected in favor of the alternative hypothesis).

9.3. Secondary Endpoints

Each secondary endpoint will be summarized and reported descriptively to characterize outcomes with treatment in the study population using the general principles described in **section 7**. No formal hypothesis testing is planned *a priori* for the secondary endpoints; hence, methods of controlling familywise Type I error (e.g., hierarchical testing, multiplicity adjustment) need not be employed.

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10. Sample Size

Based on the performance goals and hypothesis testing specified above in **section 9**, sample size and power were computed using SAS version 9.4 PROC POWER, assuming an exact test of a single binomial outcome against a performance goal (the null hypothesis). Postulating a primary effectiveness success rate of 95% against a null hypothesis of 87% per the performance goal, a sample size of 108 subjects provides 83% power to meet the primary effectiveness endpoint. Similarly, a primary safety event rate of 5% against a null hypothesis of 13% per the performance goal gives an identical sample size of 108 for 83% power.

Under modest assumptions for missing data on study outcomes (e.g., 5% missingness), to obtain 108 evaluable samples a total of 114 subjects are required to be included in endpoint analyses using the definition of enrollment (release of the GPX Embolic Material into the patient) stated above.

11. Additional Analyses

11.1. Subgroup Analyses

All subjects will be treated with the GPX Embolic Device. While their embolizations will involve different anatomical targets, each embolization procedure will still be undertaken with the desire for distal penetration. Subgroup analysis will be completed to analyze the use of the GPX Embolic Device for specific clinical applications.

Specifically, the following subgroup analyses for the primary endpoints are intended for the FAS population and will be used to determine whether covariates can modify the treatment effect of the investigational device. Statistical methods will follow the same as those outlined for poolability of sites (**section 11.3**). Subgroups of interest include the following:

- Age (≥65 years vs. <65 years)
- Ethnicity (Hispanic vs. Non-Hispanic)
- Portal Vein Embolization (Yes vs. No)
- Pre-Existing Liver Disease (Yes vs. No)
- Race (White, Asian, Black, Other)
- Renal Embolization (Yes vs. No)
- Vascular Tumors (Yes vs. No)
- Sex (Male vs. Female)

The following subgroups of those patients specifically with vascular tumors (i.e., subgroup of subgroups) are also of interest:

- Renal Angiomyolipoma (Yes vs. No)

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- Renal Cell Carcinoma (Yes vs. No)
- Bone Metastases (Yes vs. No)
- Bleeding Tumors (Yes vs. No)

Additional subgroups may be examined, but those specified above are of *a priori* clinical interest. The results of any subgroup analysis not prespecified in the protocol and SAP will not be presented in the labeling of the investigational device.

11.2. Interim Analysis

No formal interim analysis for the purpose of early stopping for effectiveness will be performed, and hence no alpha-spending will be invoked. Analysis for the purpose of evaluating study progress and/or safety which do not require alpha spending may be performed, including analyses of baseline and outcome data.

11.3. Pooling of Data

As this investigation is a multicenter study, poolability of the primary effectiveness endpoint will be assessed by testing for heterogeneity of treatment effect by clinical site of enrollment. As the primary endpoints are binomial variables, such testing will be accomplished using Pearson's chi-square test to assess heterogeneity among sites. For this purpose, sites enrolling fewer than 5 subjects will be amalgamated into a single meta-site. A resulting p-value less than 0.15 will be cause for investigation of potential causes of heterogeneity across clinical sites.

12. Changes in Planned Analyses

Any deviations or changes from this SAP deemed necessary due to changes in clinical understanding of relevant outcomes; violation of critical underlying statistical assumptions; or missing data will be clearly described with justification and rationale.

13. Revision History

Revision	DCO#	Date	Revision Description
A	2024-05-007	5/30/2024	Initial release.

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