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Statistical considerations in protocol development related with NIH protocol templates

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Objectives

- To translate scientific hypotheses into statistical design elements: study design, primary outcomes, statistical hypotheses, sample size calculation, and statistical analysis plan.
- To understand the difference between a scientific hypothesis and a statistical hypothesis.
- To review statistical items in NIH protocol templates at https://irbo.nih.gov/confluence/display/ohsrp/Protocol+Templates

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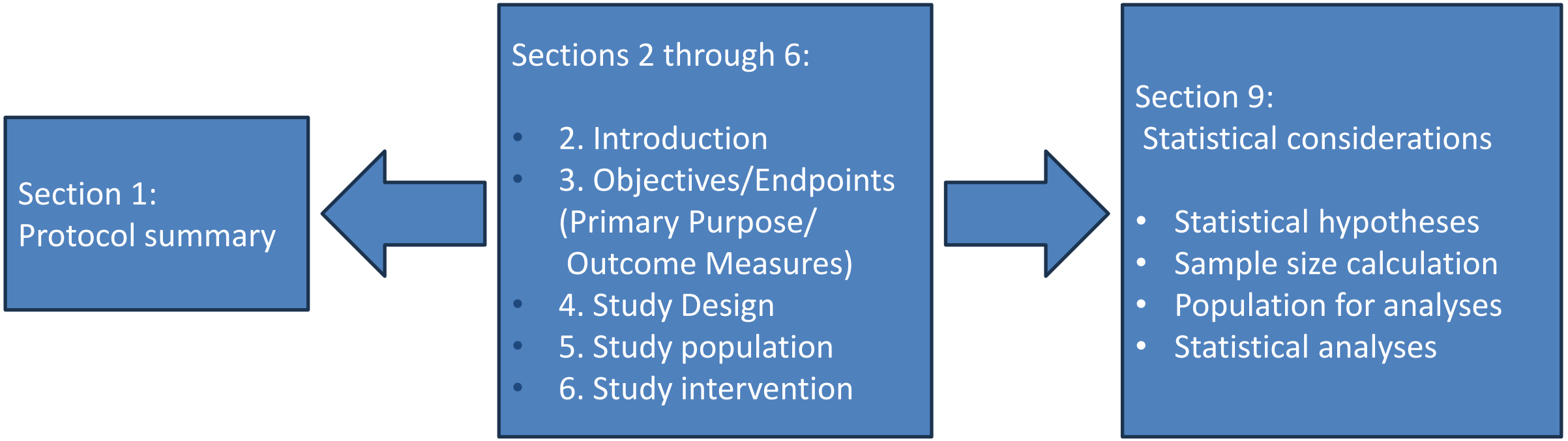
Structure of protocol template



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Section 9 Statistical considerations

- To describe statistical design elements: statistical hypotheses based on study design and primary/secondary outcomes, sample size calculation, populations for analyses and statistical analyses.
- Whether Statistical Analysis Plan (SAP) is developed.
- If SAP will be developed, the subsections below can be described in SAP in detail and summarized in Section 9.
- SAP should be completed prior to database lock and unblinding/data analysis of study data.

Statistical hypotheses	Sample size calculation	Population for analyses	Statistical analyses

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Section 9 Statistical considerations, cont.

- Statistical hypotheses:
  - Need clear, and well-defined study objective
  - Identify key variables such as dependent/independent variables from primary/secondary outcomes and interventions/groups
  - Determine type of hypothesis : Null/Alternative hypothesis, Simple/Composite
  - Specify directionality : one-sided or two-sided
  - Check testability : Statistical methods and their underlying assumptions, sample size calculation

- Sample size calculation :
  - Alpha of 0.05, Power of 80%
  - Specify effect size
  - Statistical method
  - Consider dropout and withdrawal to have a requested sample size

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Section 9 Statistical considerations, cont.

- Population for analyses:

Intention-to-treat (ITT): All randomized subjects	Modified intention-to-treat: subset of ITT by adding more restriction	Per-Protocol: subset of subjects, e.g., who took at least 80% study intervention	Safety: subset of subjects for whom safety analyses will be conducted
	Subjects who received at least one of study intervention	Subjects who completed the study intervention	Subjects who took at least one time of study intervention

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Section 9 Statistical considerations, cont.

- Statistical analyses
  - State how baseline demographic/clinical variables are reported.
  - For statistical inferences, indicate significance level, one-sided or two-sided.
  - Indicate/Prespecify whether covariates/factors will be included.
  - Analysis of primary endpoints
  - Analysis of secondary endpoints
  - If interim analysis is planned, describe it in detail in protocol or SAP.
  - Sub-group analyses: need to be pre-specified.
  - Safety analysis: describe how to analyze safety outcome such as incidence of adverse events (AEs) /serious AEs
  - Exploratory Analyses: need to be pre-specified

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Conversion of study objective to statistical hypothesis

- Example 1 : Fluid Balance and Body Weight Changes in Critically Ill Adult Patients (NCT04434079)
  - Study population : Adults patients admitted to Incentive care unit (ICU) between Jun-Oct 2018 if expected length of stay ≥ 24 hours without oral nutritional.
  - Intervention type : Other
  - Prospective observational study
  - Single arm
  - Primary outcome :

    Correlation between daily fluid balance (FB) and daily body weight (BW) change
  - Secondary outcomes :

    Correlation between cumulative FB and total BW change

    Discriminative power of FB in predicting ICU mortality using Area under ROC* curve

    Discriminative power of BW change in predicting ICU mortality using Area under ROC* curve

*Receiver Operating Characteristic (ROC)

- Example2 : Processed Food and Energy Intake (NCT03407053)

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Section 9 Statistical considerations, revisited.

- Statistical hypotheses:
  - Need clear, and well-defined study objective
  - Identify key variables such as dependent/independent variables from primary/secondary outcomes and interventions/groups
  - Determine type of hypothesis : Null/Alternative hypothesis, Simple/Composite
  - Specify directionality : one-sided or two-sided
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Conversion of scientific objective to statistical hypothesis, cont.
Example 1 : NCT04434079

- Study objective : To compare the measurements of Fluid balance (FB) and body weight (BW) over time and to assess correlation with ICU mortality.

- State scientific hypothesis :
  1. To examine correlation between FB and BW change measured every 24 hours of patients in ICU.
  2. To examine the effect of FB/BW change to predict ICU mortality using Area under ROC curve

- Identify key variables :
  1. No dependent and two independent : FB and BW change
  2. Dependent/Independent : Mortality/ either FB or BW change

- Determine type of hypothesis : Null and alternative hypotheses with two-sided
  1. Null : there is no correlation between FB and BW change
     Alternative : there is correlation between FB and BW change
  2. Null : Area under ROC curve = 0.5
     Alternative : Area under ROC curve ≠ 0.5

Conversion of scientific objective to statistical hypothesis, cont. Example 2 : NCT03407053

- Primary aim from protocol: To determine differences in ad libitum energy intake (kcals) during 2 weeks of eating an ultra-processed diet as compared to 2 weeks of an unprocessed diet matched for presented calories, macronutrient composition, sugar, fiber, and sodium.

- State scientific hypothesis :

  To examine difference on averaged as libitum energy intake between two diets

- Identify key variables :
  - Dependent : type of diet
  - Independent : averaged as libitum energy intake

- Determine type of hypothesis : Null and alternative hypotheses with two-sided
  - Null hypothesis : there is no difference between the two diets (μ_d*=0)
  - Alternative hypothesis : there is difference between the two diets ($\mu_d \neq 0$)

  *μ_d : mean of difference in averaged ad libitum energy intake between two diets

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What is Statistical Analysis Plan (SAP)?

- Provides more technical and comprehensive details of statistical modeling of outcomes additional to key points of statistical analysis in Section 9.
- Pre-registration of outcomes, statistical hypotheses, and statistical method.
- Develop SAP along with protocol development simultaneously through a collaboration between investigators and statisticians.
- Can be revised with SAP version number and reason for each revision.
- Must be completed before database lock for observational studies or unblinding/analysis of study data in interventional studies.

- SAP is required for clinical trials along with the protocol in CT.gov when results is reported.
- NIH grant applications for interventional studies require SAP.
- Many journals such as NEJM/JAMA request SAP for publication of clinical trials.

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Statistical Analysis Plan (SAP), cont.

- Additional key items:
  - Detailed description when more complicated statistical model is planned: continual reassessment method for dose finding studies.
  - Describe method for controlling inflated type I error in multiple comparison with outcomes/subgroups.
  - Pre-specification of confounding variables.
  - Describe how to handle missing data.
  - Address/minimize: publication bias (selective reporting), selection bias (exclude sicker patients), measurement bias (measurement error).

- Benefit:
  - Reproducibility of results by having transparency in statistical methodology in data analyses
  - Increase efficiency at time of data analysis by improving clarity in communications between statistician and investigator
  - Reduce the risk of data-driven results by preventing pvalue-hacking/ data-dredging

- Time consuming to develop SAP on the front

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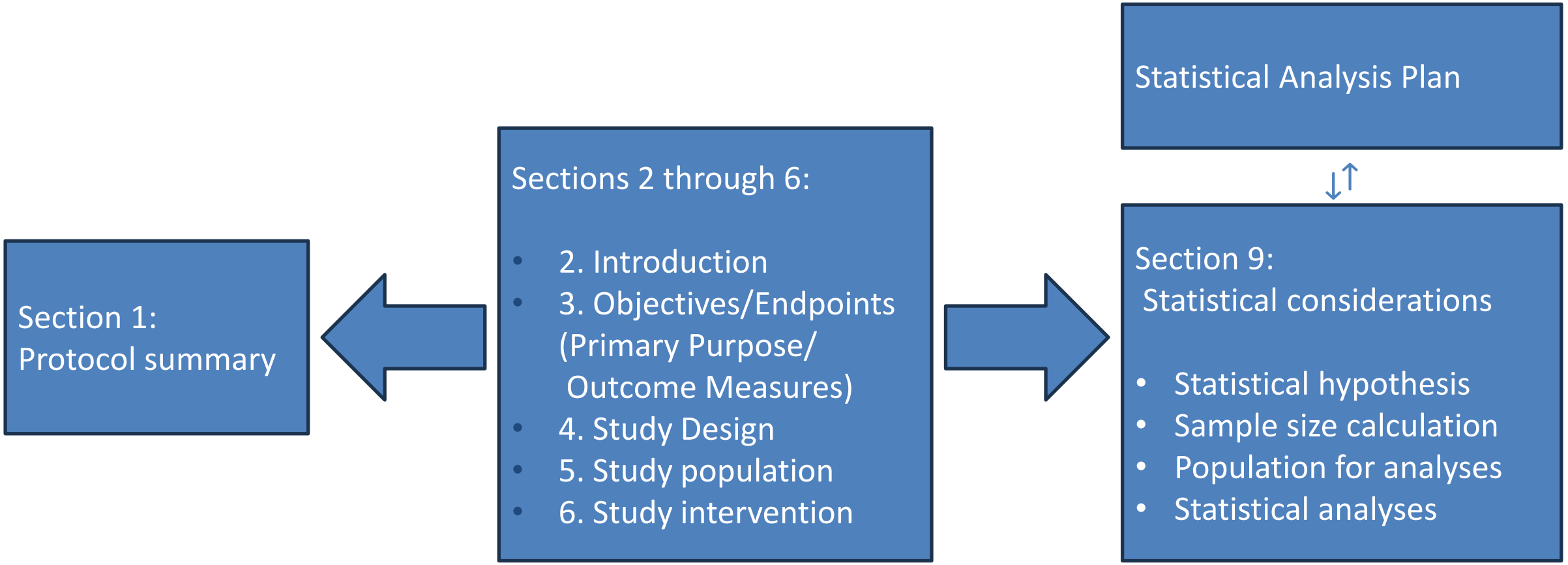
What can be added/discussed in SAP in Example 1, revisited

Dependent	Independent	Null hypothesis	Alternative hypothesis
	FB, BW change	no correlation between FB and BW change	correlation between FB and BW change
Mortality	FB	Area under ROC curve = 0.5	Area under ROC curve ≠ 0.5
Mortality	BW change	Area under ROC curve = 0.5	Area under ROC curve ≠ 0.5

- Definition of primary/secondary outcomes: mixed with outcome and test statistic
- Statistical method for mortality
- Discuss possibility of including covariates such as severity of disease, type of disease, and baseline BW when FB is used for mortality analysis
- Survival analysis can be used for examine the effect of FB/BW change on mortality

Structure of protocol template



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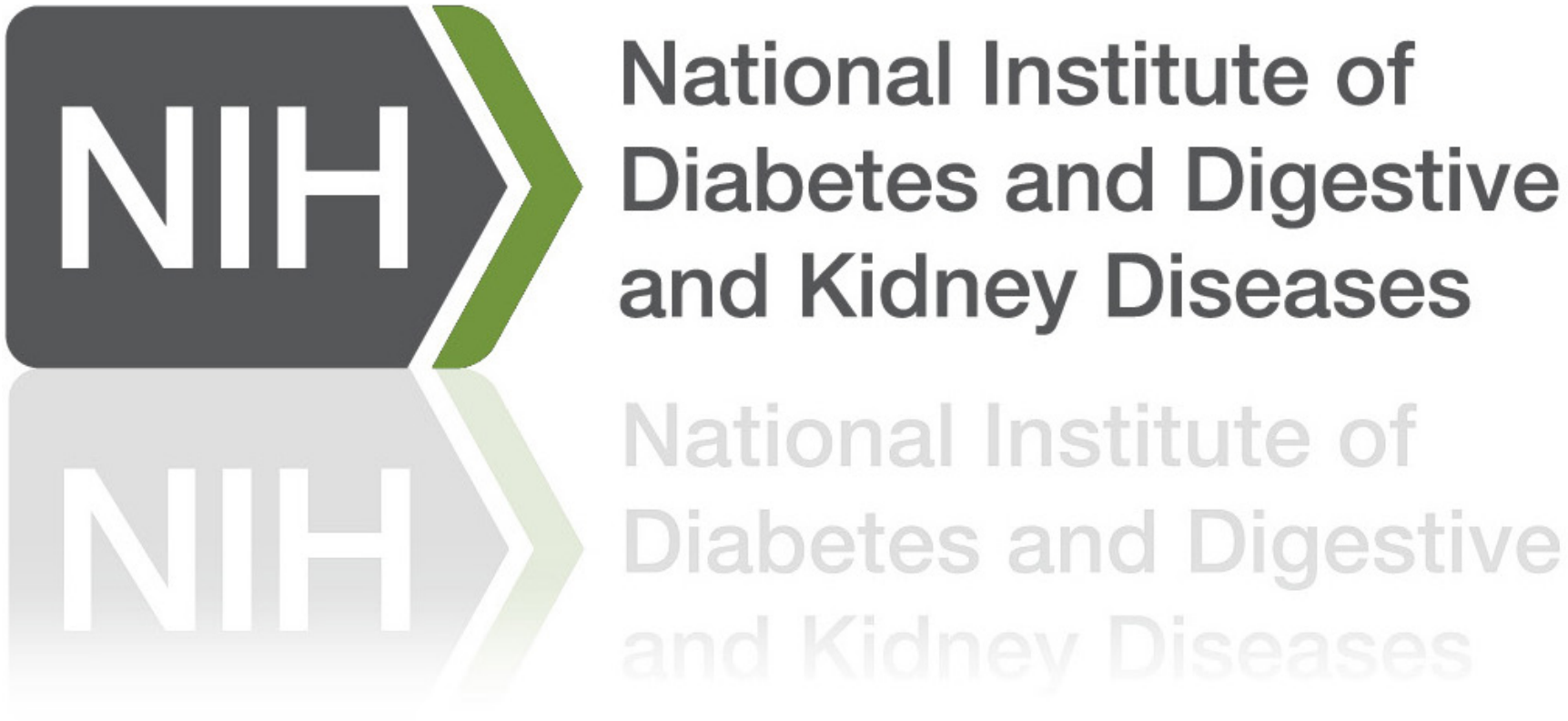
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