Study Designs and Endpoints (Outcomes)

In Protocols and on ClinicalTrials.gov

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July 17, 2025

Outline

- What is ClinicalTrials.gov (CTG)?
- Describe CTG design elements and how do they relate to protocols
  - Use 3 NIDDK studies as examples
- How are endpoints (outcomes) defined in protocols and CTG?
- How are results reported to CTG?
- Example of results reported for 1 NIDDK study

What is ClinicalTrials.gov?

- ClinicalTrials.gov (CTG) is a website and online database of clinical research studies.
- Its purpose is to provide information about these studies to the public, researchers, & health care professionals.
- Launched in 2000, required by federal laws
- Maintained by the NIH National Library of Medicine (NLM).
- Currently lists 544,024 studies with locations in 229 countries.
- https://clinicaltrials.gov/about-site/about-ctg

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What are the benefits of ClinicalTrials.gov?

- Registration data can be used
  - to identify similar studies during protocol development,
  - to find studies for systematic reviews and meta-analyses,
  - to find study publications (automatically linked by NCT number).
- Results data can be used
  - for sample size estimates (means and SD),
  - for meta-analyses,
  - to supplement results reported in publications for studies with many secondary outcomes

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Example of using CTG to plan a study

	Study Title	NCT Number	Status	Conditions	Interventions	Sponsor	Study Type
1	Glucokinase Activator in Monogenic Diabetes New	NCT06976658	Not yet recruiting	• Diabetes Mellitus • Monogenic Diabetes	• Drug: Dorzagliatin • Drug: matched placebo	Chinese University of Hong Kong	Interventional
2	Chronic Dorzagliatin on Insulin and Incretin Function in Intermediate Hyperglycemia and Type 2 Diabetes	NCT06671340	Not yet recruiting	• Diabetes Mellitus • Prediabetes / Type 2 Diabetes	• Drug: Dorzagliatin	Elaine Chow	Interventional
3	Cardiometabolic Benefit of Reducing Iatrogenic Hyperinsulinemia Using Insulin Adjunctive Therapy in Type 1 Diabetes	NCT06609356	Recruiting	• Type 1 Diabetes Mellitus • Glucokinase-Maturity Onset Diabetes of the Young (GCK-MODY)	• Procedure: Study Visit 1 • Drug: Placebo • Procedure: Study Visit 2 • 1 more	Vanderbilt University Medical Center	Interventional

https://www.clinicaltrials.gov/search?term=mody2
36 studies, 30 interventional, 22 completed, 6 with results
Study descriptive data can be downloaded as a csv file (30 items)
Complete data: https://aact.ctti-clinicaltrials.org/ analyze using R or SAS

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Which studies should be registered on CTG?

	Register	Report Results
All clinical trials (most medical journals)	X	
Clinical trials of drugs, biologics, & devices regulated by FDA, except phase 1	X	X
NIH funded clinical trials (2017 or later)	X	X
NIH IRP observational studies	X	

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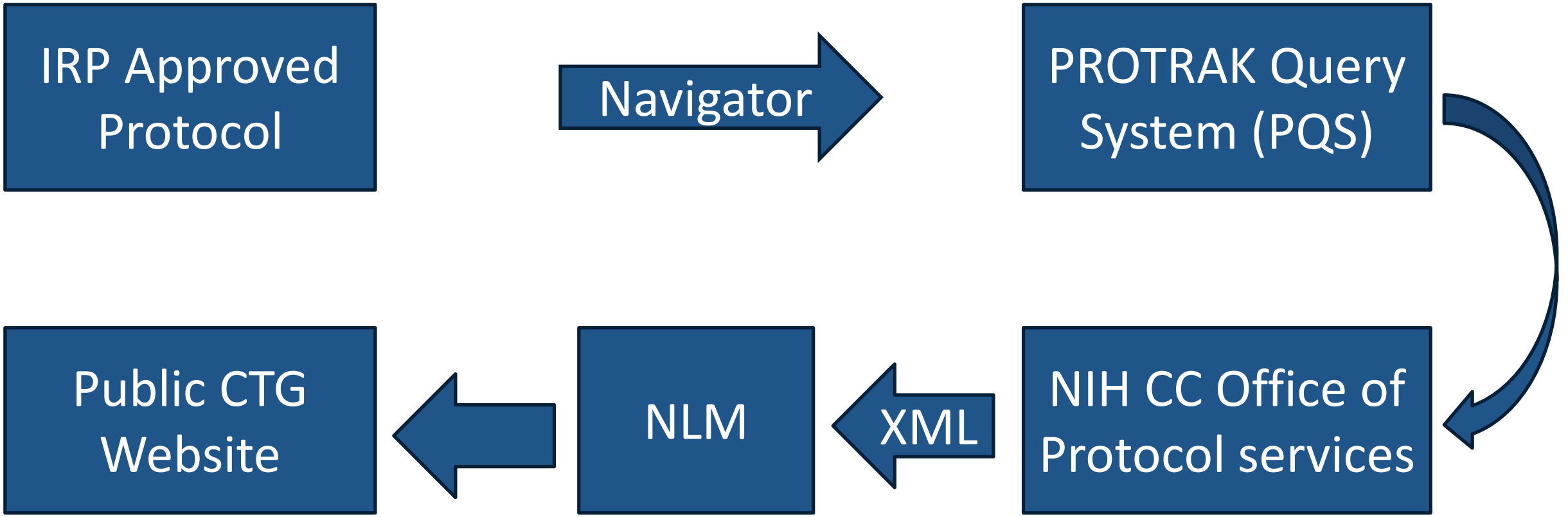
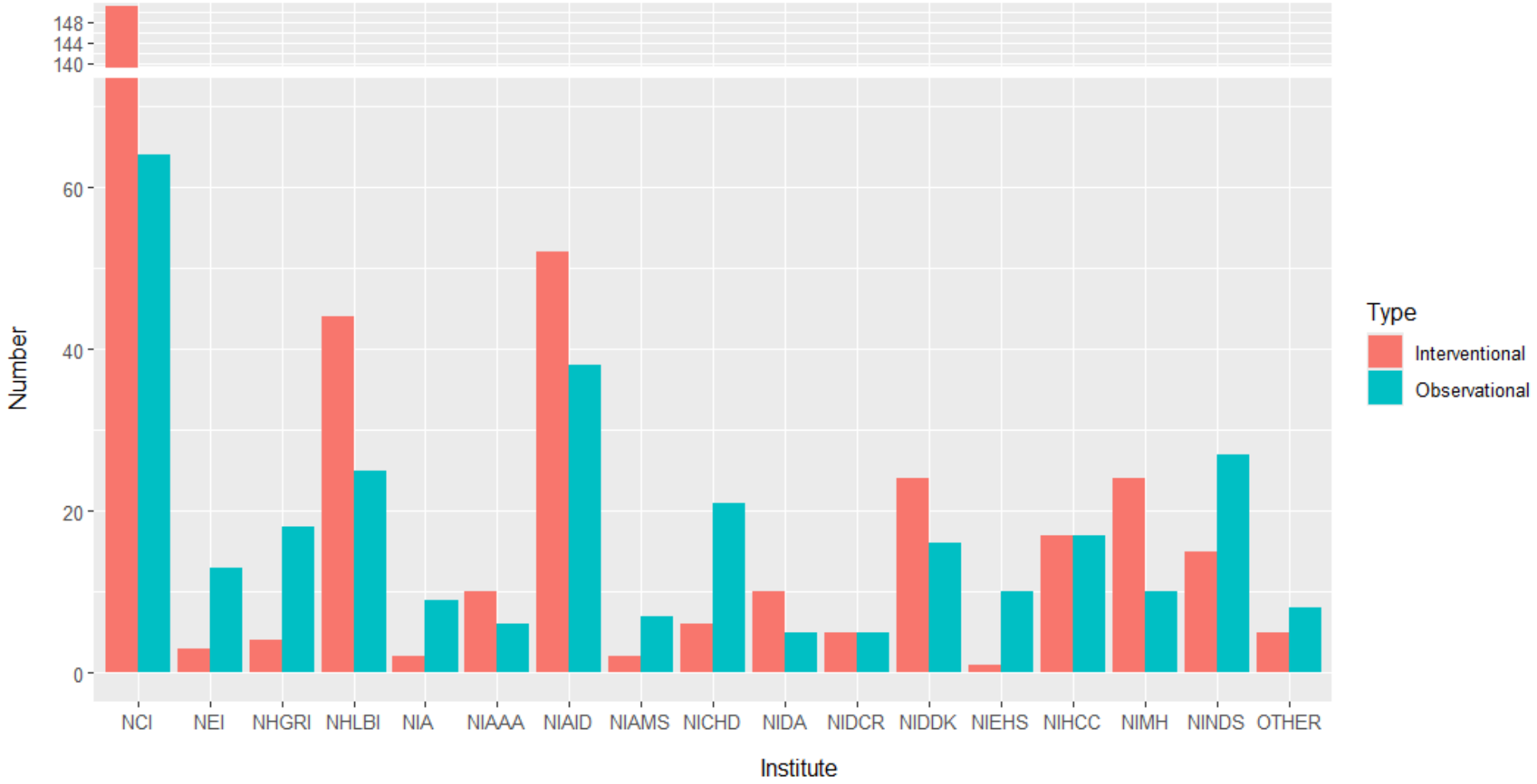
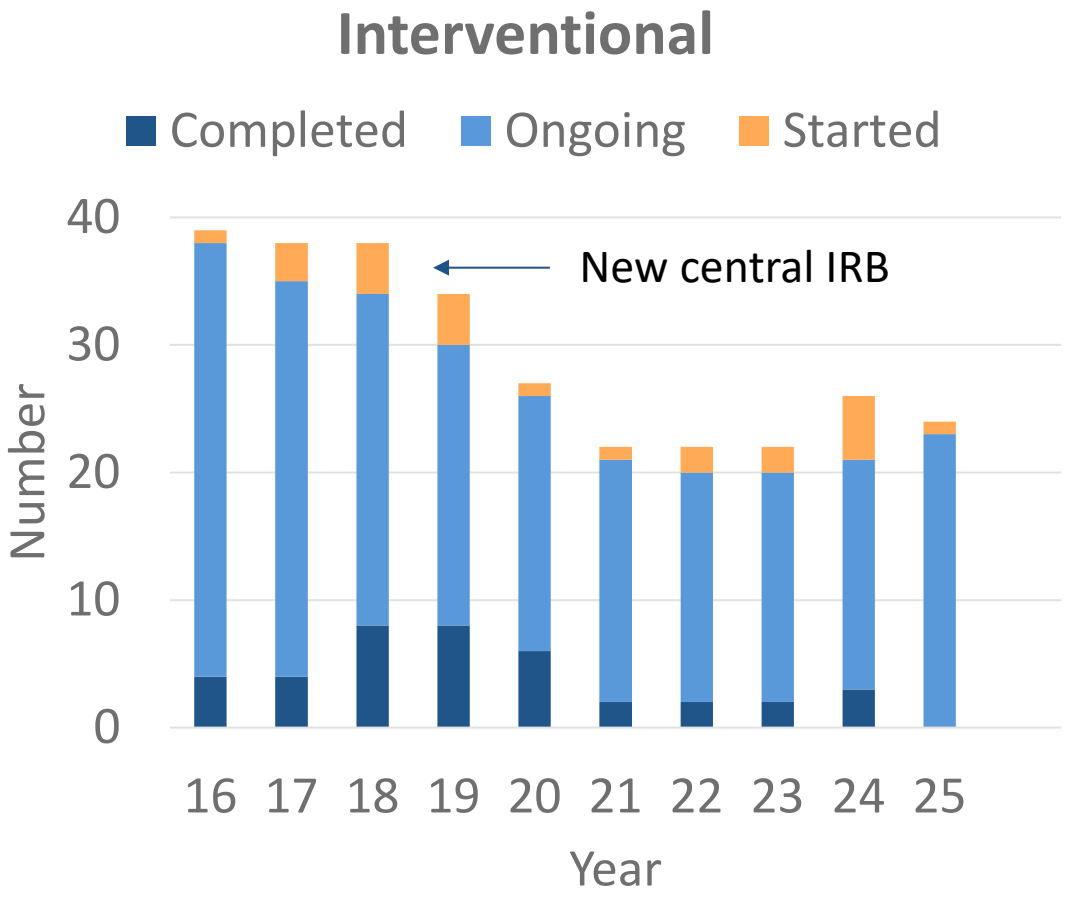
How are NIDDK IRP studies registered on CTG?

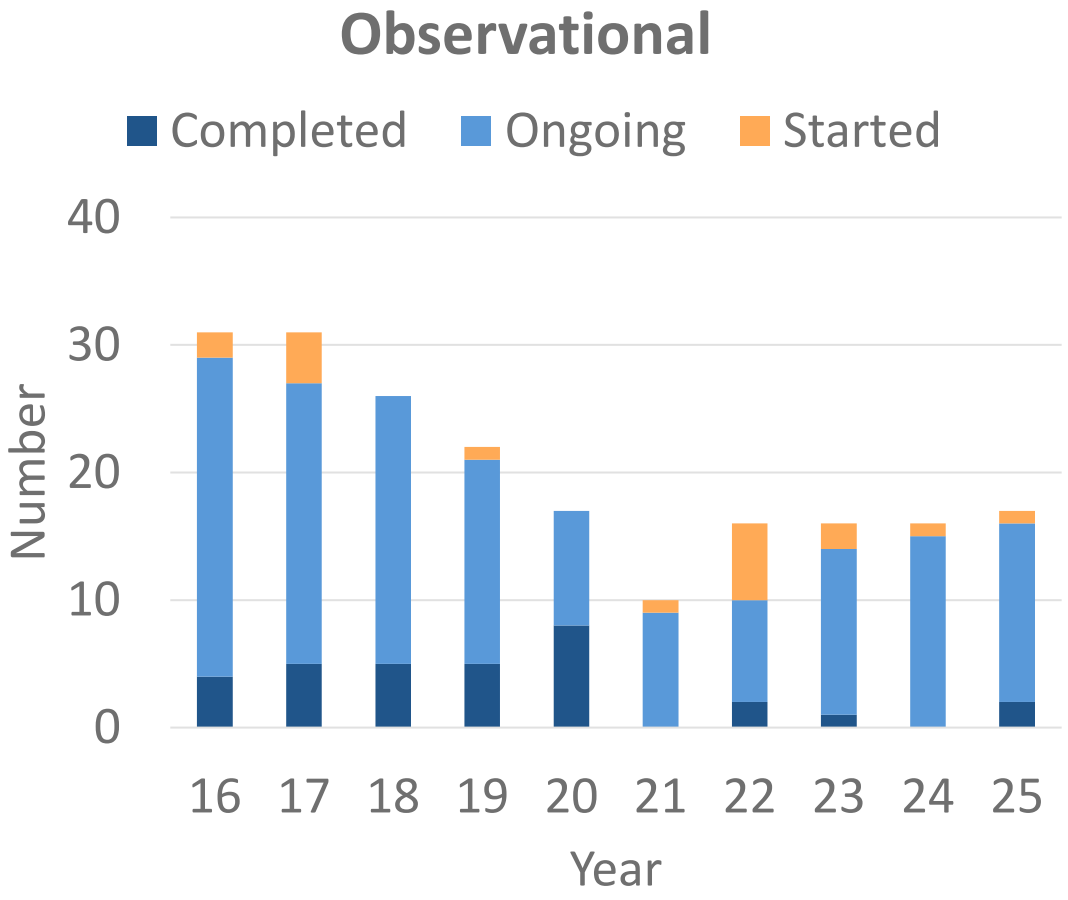


NIH IRP active studies as of 5/30/2025



NIDDK IRP active studies 2016 – 2025





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What study information is included on CTG?

- Type of study – investigational or observational
- Study name and description, disease or health problem
- Start and end dates, enrollment, study status (recruiting, etc.)
- Eligibility criteria and design (single arm, randomized)
- Interventions, arms or groups, and outcome measures
- Links to publications, with automatic links to PubMed if NCT number is in publication abstract

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Interventional study model options

- Single: A group of participants receiving the same intervention
- Parallel: Pts assigned to 2+ groups (populations) or arms (interventions) for the duration of the study
- Crossover: Pts assigned to one intervention and then a second, usually in random order.
- Factorial: Pts assigned to 2+ interventions, each alone and in combination
- Sequential: Pts progress from 1 treatment to next if meet criteria.

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Arms and interventions on CTG

Arm types

- Experimental
- Comparator
  - Active
  - Placebo
  - Sham (for procedures or devices)
- No Intervention
- Other

Intervention types

- Drug: Including placebo
- Device: Including sham
- Biological/Vaccine
- Procedure/Surgery
- Radiation
- Dietary supplement
- Other (includes diets)

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Three NIDDK examples

- Processed Food and Energy Intake
  - Effect of Ultra Processed Versus Unprocessed Diets on Energy Intake, 18DK0044 (NCT03407053), 3/1/2018 – 2/26/2020
- Pegvisomant in Insulin Resistance
  - Study of Growth Hormone Inhibition Using Pegvisomant in Severe Insulin Resistance, 000765 (NCT05470504), 1/23/2023 – 1/31/2026
- Nicotinamide Riboside and Ketone Metabolism
  - Effect of Nicotinamide Riboside on Ketosis, Fat Oxidation & Metabolic Rate, 001690 (NCT06044935), 1/8/2024 – 1/31/2026

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Processed Food and Energy Intake

Design, arms, and outcomes

- Randomized, 2 arm cross-over design
- Arm 1: Ultra-processed followed by unprocessed
- Arm 2: Unprocessed followed by ultra-processed
- For reporting outcomes and AEs, the arms are the interventions
- Primary outcome: Ad libitum energy intake averaged over 14 days for each diet

Study schema

Pegvisomant in Insulin Resistance Schema

Design, arms, and outcomes

- Single arm trial
- Drug intervention
- Primary outcomes:
  - Change in glycerol rate of appearance (Ra) normalized to fat mass
  - Change in palmitate Ra normalized to fat mass

Study Schema

VISIT 1 (Day: -2 to 0)

3 Day Inpatient Visit
Metabolic Testing
Start pegvisomant by daily sc injection

Weekly Telephone Check-in (~ Days 7, 14, 21)

Review adverse events
Review study drug compliance
Day ~14 check liver function tests

VISIT 2 (~Day 28-31)

3 Day Inpatient Visit
Metabolic Testing
Review adverse events
Review glucose logs

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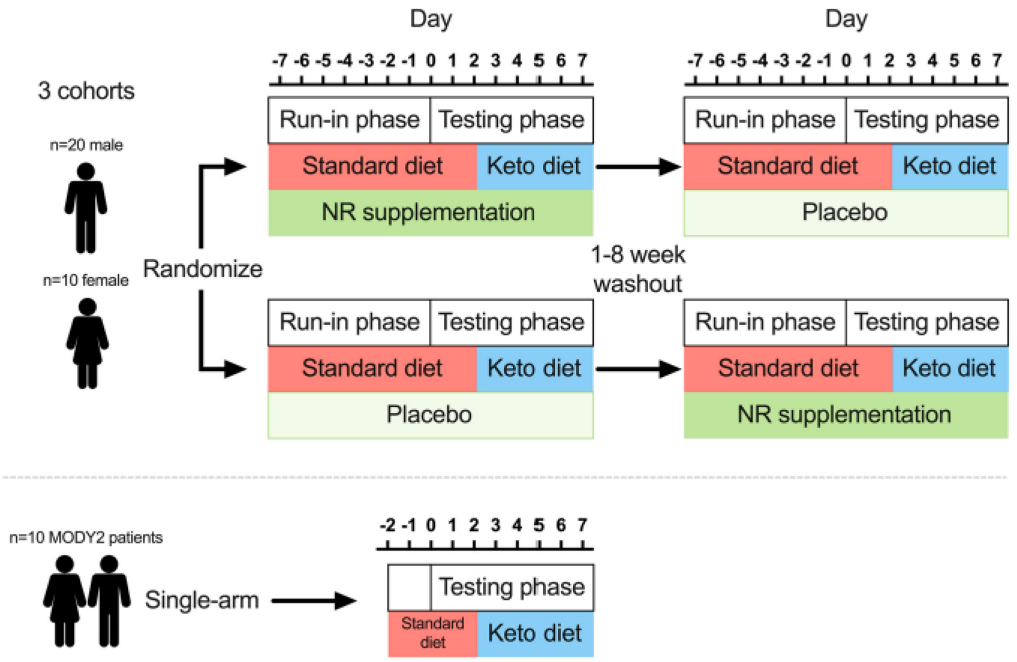
Nicotinamide Riboside and Ketone Metabolism

Designs, arms, and outcomes

- 3 cohorts (2 crossover design, 1 with a single group design)
- Interventions
  - standard diet, ketogenic diet
  - Nicotinamide Riboside (diet. supp.)
  - Placebo (dietary supplement)
- Primary outcomes
  - Change in sleeping energy expenditure between run-in and ketogenic diets
  - Difference in sleeping energy expend. between NR and placebo during keto diet

Study schema



How are outcome measures reported on CTG?

- Endpoints in protocols are called outcomes on CTG.
- The following is required for each outcome on CTG:
  - Specify as primary or secondary (tertiary are usually not included)
  - Each measurement is a separate outcome, for example, fasting LDL cholesterol, not lipid panel,
  - Time frame, for example, baseline and 6 weeks,
  - Questionnaire outcomes must include a description of scores,
  - Descriptions should not include hypotheses or analyses,
  - Outcome can be a summary measure, for example, correlation.

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When do results have to be reported?

- Results for clinical trials must be reported within 1 year of the primary completion date.
- The primary completion date is the last date that data are collected from participants for all primary outcomes.
- It is not the date that measurements become available for analysis, for example, measurements by a central laboratory.
- Results must be reported within 1 year even if publications are still being drafted.

How are results submitted for IRP studies?

- When PQS is updated to say that the primary completion date has been reached, an email is sent to the PI and to NIDDK OCD.
- The PI is given access to the Protocol Registration and Results System (PRS) for the trial and the PI can enter results
- Biostatistics program staff can assist with entering results.
- As shown on the following slides, sometimes outcomes need to be revised to meet results reporting criteria.

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Outcome title too long (aim not endpoint)

Original Outcome

- Title: 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.
- Time Frame: Ongoing
- Description:

NCT03407053

Revised Outcome

- Title: Ad Libitum Energy Intake
- Time Frame: 14 days
- Description: Ad libitum energy intake averaged over 14 days for each diet, measured in kilocalories (kcal) per day.
- Measure type: Mean (SE)
- Units: kcal/day

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Outcome measure needs more detail

Original Outcome

- Title: Ability to tolerate drugs at the prescribed dose for the full course of therapy
- Time Frame: 6 months
- Description:

NCT03600714

Revised Outcome

- Title: Number of Participants Who Discontinue Medication
- Time Frame: 24 weeks
- Description: Discontinuation of the medication before 24 weeks by the clinical team or patient will be considered a failure to tolerate the medicine.
- Measure type: Count of participants
- Units: Participants

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Example of gene expression data

Original Outcome

- Title: Changes in interferon stimulated genes during therapy with asunaprevir and daclatasvir
- Time Frame: 4 weeks on treatment
- Description:

NCT01888900

Revised Outcome

- Title: Changes in Interferon Stimulated Genes in the Liver
- Time Frame: Baseline and 2 or 4 weeks
- Description: Changes obtained by subtracting follow-up from baseline. Raw gene expression data were normalized using quantile normalization based on all the genes
- Measure type: Median (IQR)
- Units: Relative expression

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Example of correlation data

Original Outcome (first registration)

- Title: To determine correlations between D2BP, as measured by [18F]fallypride and [11C]raclopride time-activity curves
- Time Frame: Ongoing
- Description:

NCT03648892

Revised Outcome (results)

- Title: Correlation Between Striatal D2 Receptor Binding Potential (D2BP) as Measured by [18F]Fallypride and [11C]Raclopride Time-activity Curves
- Time Frame: Assessed at Days 2-5
- Description: Pearson's correlation coefficient is used with a possible range between -1 to 1.
- Measure type: Number (95% CI)
- Units: Correlation coefficient

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Participant flow

Arm/Group Title	Metformin	Metformin and Liraglutide
Period Title: **Overall Study**		
Started	13	11
Completed	12	10
Not Completed	1	1
Reason Not Completed		
Withdrawal by Subject	1	0
Poor compliance	0	1

Therapeutic Targets in African-American Youth With Type 2 Diabetes, 17DK0013, NCT02960659

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Baseline characteristics

Arm/Group Title	Metformin	Metformin and Liraglutide	Total
Age, Continuous Mean (Standard Deviation) | Unit of measure: Years			
Number Analyzed	13 participants	11 participants	24 participants
	15.6 (2.1)	15.0 (2.1)	15.3 (2.1)
Sex: Female, Male Measure Type: Count of Participants | Unit of measure: Participants			
Number Analyzed	13 participants	11 participants	24 participants
Female	8 61.5%	7 63.6%	15 62.5%
Male	5 38.5%	4 36.4%	9 37.5%

Outcome measures

1. Change in Absolute Gluconeogenesis From Baseline to 12 Weeks

Type: Primary | Time Frame: Baseline to 12 weeks

Description	Gluconeogenesis is measured using stable isotope tracers and is reported as mg/kg lean body mass (LBM) per minute	
Time Frame	Baseline to 12 weeks	
Analysis Population Description	Data are missing for one patient in the Metformin group due to technical difficulties	
Arm/Group Title	Metformin	Metformin and Liraglutide
Overall Number of Participants Analyzed	11	10
Mean (Standard Deviation) | Unit of Measure: mg/kg LBM/min	0.018 (0.34)	-0.050 (0.24)

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Adverse events

Other (Not Including Serious) Adverse Events				
Frequency Threshold for Reporting Other Adverse Events	0%			
Arm/Group Title	Metformin		Metformin and Liraglutide	
	Affected / at Risk (%)	# Events	Affected / at Risk (%)	# Events
Total	6/13 (46.15%)		7/11 (63.64%)	
Gastrointestinal disorders				
Abdominal pain *	1/13 (7.69%)	1	2/11 (18.18%)	2
Diarrhea *	2/13 (15.38%)	3	2/11 (18.18%)	2
Nausea *	1/13 (7.69%)	1	1/11 (9.09%)	1
Vomiting *	0/13 (0.00%)	0	3/11 (27.27%)	4

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Summary

- CTG is a useful resource for study planning
- CTG formatting requirements provide a framework for specifying study design and outcomes
- Links
  - https://clinicaltrials.gov/policy/protocol-definitions
  - https://clinicaltrials.gov/policy/results-definitions

- Questions?

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